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CARDIAC PAIN AND ITS SIGNIFICANCE*

BY JAMES ALEXANDER LYON, M.D.†

THE high death rate from heart disease, revealed by recent mortality records, has fixed public attention upon the heart as a cause of death. A disproportionate amount of this publicity has fallen upon angina pectoris and coronary thrombosis, whose dramatic syndromes occasionally take the front page with the sudden death of a prominent citizen. To the patient, pain in the region of the heart has come to mean angina pectoris. More than one such patient has, upon close questioning, been found to have a very good general idea of the anginal syndrome, into which he was attempting to fit his own symptoms.

The demonstration of absolute ischemia of the heart muscle in coronary occlusion and the widespread acceptance of the theory of relative ischemia of the heart muscle in angina pectoris have focused the attention of the medical profession upon what is considered the common basis of the two conditions, namely, coronary arterial disease. When a patient in the middle or later years of life presents himself for examination complaining of heart pain, the physician, aware of the possibility of a later coronary occlusion, hesitates to rule out angina pectoris even though the symptoms are somewhat atypical, especially when the physical signs and the electrocardiogram suggest coronary disease. No doubt there has been need of a more alert and painstaking recognition of angina pectoris. My experience in recent years, however, has led me to question whether we are not becoming overcautious.

A man in the sixties came under my observation with a diagnosis of angina pectoris made six years before, at which time he had been given a vial of nitroglycerin. The physical examination required a half hour, during all of which time the patient complained of severe precordial pain. There was no pallor of the skin and no moisture on the forehead; his face was slightly flushed. After the completion of the examination a hypodermic tablet of nitroglycerin, grains 1/100, was put under his tongue. He instantly expressed himself as relieved of pain. There was no gradual subsidence of the pain and no lapse of the required time for the drug to take effect. Over the six-year period following the diagnosis of angina pectoris the patient had been taking fifteen to twenty tablets of nitroglycerine daily. This man was extremely active in his profession and was under severe mental pressure. The diagnosis of angina pectoris had considerably augmented the strain under which he was working. This individual may possibly die of coronary occlusion—many professional men in the sixties and seventies do—but up to the present time he has not, I believe, had an attack of angina pectoris. Only recently this opinion was concurred in by the staff of one of our large and well-known hospitals.

A young woman, forty-four years of age, consulted me six months ago with a diagnosis of angina pectoris. At the time the diagnosis was made she was warned against walking up and down stairs and was advised to give up all social activities. Over a period of a year and a half, during which she followed this regimen, she remained unimproved. It was found, when a careful history was taken, that this was a very definite and precise case of a patient suffering from neurocirculatory asthenia. Under encouragement, assurance that she did not have angina pectoris and a progressive return to her former activities and mode of living she gradually returned to normal health.

The following case, quoted from an article presenting atypical cases of angina pectoris, illustrates our present-day reluctance to diagnose pain in the region of the heart by any other term than angina pectoris.

"A man, aged sixty, with arterial hypertension, had as his sole complaint pain in the shoulders, radiating upward into the posterior cervical region toward the occiput. Although he was somewhat short of breath on exertion and had premature ventricular beats, his pain practically never occurred except early in the morning when he bent over the wash bowl to bathe his face and neck. The *anginal* nature of these discomforts was tragically demonstrated when he died suddenly one morning while bathing, probably of coronary occlusion."

The assumption in this case that the pain was anginal in nature because the patient suffered sudden death ignores two facts. First, coronary occlusion may occur without angina pectoris as a forerunner and, secondly, an individual, particularly one past middle age, may have two coincident but unrelated diseased conditions. Fixing a diagnosis of angina pectoris on any pain in the region of the heart that precedes sudden death from probable coronary occlusion makes the atypical all inclusive, gives equal significance to every type of cardiac pain and confuses diagnosis.

There are three sets of diagnostic criteria inherent in the classical Heberden syndrome. One concerns the nature of the exciting cause of an attack; another is the location and quality of

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†Lyon, James A.—Professor of Clinical Cardiology, Georgetown University School of Medicine, Washington, D. C. For record and address of author see "This Week's Issue," page 991.

the pain; a third is the manner and the conditions under which the pain subsides.

When the syndrome follows the classical pattern, the attack is precipitated by a fairly constant amount of exertion or emotional excitement, although the amount necessary to induce pain may gradually lessen over a period of time and may be less following the ingestion of food. If a patient complains of having an attack of heart pain whenever he exerts himself in such a way as to involve a particular movement of the head, shoulders or spine and is free of attacks when undergoing other kinds of exertion requiring the same degree of effort, he very probably does not have angina pectoris. There is a possibility that careful roentgenologic studies in such a case would show spondylitis of the upper dorsal or cervical regions which in certain movements irritates the nerve roots directly. Or, careful questioning might elicit the presence of some of the more common symptoms of arthritis or of focal infection so that cervical arthritis or hypertrophic arthritis of the spine might be suspected.

In typical angina pectoris, the pain centers in the substernal region. This location was found by the German clinicians to be so invariable in angina pectoris that they designated it substernitis. My own experience supports the German view, and I cannot recall having seen a case of precordial pain that was diagnosed angina pectoris in which the diagnosis was not open to question on other grounds as well. There are several conditions which give rise to various types of precordial pain; but since there is a difference of opinion as to whether we can admit precordial pain into the anginal syndrome, it would seem more exact to discuss the types of precordial pain on the basis of their characteristics rather than of their location.

The pain of angina pectoris is paroxysmal with a gradual rise in intensity and a gradual subsidence. The duration of an attack is usually from three to fifteen minutes. In very mild or beginning cases the pain may be severe for only a matter of seconds. In long-continued cases or cases of anginal failure it may be intense for thirty minutes and occasional for an hour or more. When a patient is suffering prolonged attacks of pain, angina pectoris must be sharply differentiated from coronary occlusion and the patient must be watched for the possible appearance of a fall in blood pressure, an elevation of temperature, a leucocytosis and a friction rub, indicative of myocardial infarction.

A burning, boring, constricting or crunching pain is characteristic of angina pectoris; rarely, if ever, is it a sharp, knifelike or a dull, aching sensation. My experience would indicate that intermittent, sharp, stabbing precordial pain is frequently associated with aortic valvular disease. The literature shows a divergence of opinion on this point. Laplace,[1] however, noted that 82 per cent of the patients in a group of seventy-two cases of aortic valvular disease complained of this sharp, stabbing type of precordial pain. A patient may suffer from both the precordial pain of aortic disease and the substernal pain of angina pectoris, but a carefully taken history and close questioning will prevent a confusion of the two types. The short, sharp pain associated with extrasystoles is differentiated from anginal pain both by its sudden intensity and by its having no constant relation to exertion. An intense, sharp but continuous precordial pain is at times associated with paroxysmal auricular tachycardia of very rapid rate. When its duration is brief, it may simulate the pain of angina pectoris and, when its duration is prolonged, the pain of coronary occlusion. I have now under my care a woman, thirty-seven years of age, who recently had such an attack lasting four hours and not subsiding until the tachycardia ceased. The heart rate during the paroxysm was between 190 and 230 beats per minute. A sharp, fleeting precordial pain is sometimes complained of in acute rheumatic heart disease. In pericarditis there may be a sharp, stabbing pain, especially on inspiration, or a continuous severe ache, if extrapericardial tissues are involved. Pulmonary embolism not infrequently gives rise to intense, continuous precordial pain simulating that of coronary occlusion. A dull, heavy precordial ache is at times associated with hypertension, valvular disease, enlarged and failing hearts, cardiac neuroses and neurocirculatory asthenia.

The pain of angina pectoris characteristically radiates into the left shoulder and down the left arm into the little finger. Occasionally it radiates into both shoulders and rarely into the right shoulder only, into the neck or under the left scapula. At times there is no radiation. In mild or beginning cases the pain in rare instances may be confined to the area of radiation and be absent in the substernal region. In such a case the possibility of arthritis or neuritis must be considered. There are cases of undoubted angina pectoris with radiation in which the patient, during the time elapsing between seizures, experiences dull aching or burning pain in the area of radiation. It is not unlikely that we are dealing in these cases with two distinct conditions, rather than two phases of one condition. The pain of arthritis or neuritis caused by a latent focus of infection may well be localized in an area highly sensitized by the radiated pain of angina pectoris. Such a condition existed in a patient under my observation.

A patient in an anginal seizure generally

shows some pallor of the skin and moisture on the forehead. This appears in rather striking contrast to the flushed appearance of the skin when a patient is experiencing the sharp, stabbing precordial pain associated with aortic disease, and patients have repeatedly told me that they have no feeling of apprehension during their attacks even when the pain is very severe and prolonged. On the other hand, when the pain of angina pectoris is intense the patient is likely to express some degree of apprehension. Mild gastrointestinal symptoms occasionally appear during an anginal seizure, and not a few anginal patients have been treated for indigestion. It may be noted in passing that severe gastrointestinal symptoms are sometimes observed in cases of coronary occlusion and that their appearance at the onset of an attack has at times been responsible for surgical interference. The reverse is also true, for gastrointestinal upsets with referred pain in the chest have been diagnosed angina pectoris or coronary occlusion.

The subsidence of anginal pain is gradual, the intensity receding slowly when the patient comes to a standstill and more rapidly when amyl nitrite or nitroglycerin is administered. When the pain disappears the patient feels normal. There are no "hangover" symptoms, with the single exception of some slight degree of nervous exhaustion in occasional patients. No sensitiveness or tenderness to pressure is felt over the chest, as in cases of neurocirculatory asthenia and cardiac neurosis.

These personal observations on the nature of the exciting cause of an attack of angina pectoris, the location and quality of the pain and the manner and conditions under which the pain subsides have brought up for consideration only a few of the conditions that may give rise to cardiac pain. Any condition, such as eroding aneurysm, mediastinal growth or diaphragmatic pleurisy, that causes a direct stimulation of the sensory nerve endings in the thoracic wall may induce pain simulating angina pectoris. So also may certain other conditions of the chest, such as tumors, fibrotic or inflammatory lesions, herpes zoster, tabetic crises and bursitis.

During the past year, 80 per cent of the patients who presented themselves for examination in my private practice complained of cardiac pain. A few had angina pectoris, many more did not. The significance of cardiac pain can be rightly evaluated in the majority of cases only by a close, painstaking questioning of the patient designed to differentiate sharply the various types of pain.

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A SCHEME FOR THE TREATMENT OF DIABETES MELLITUS WITH HIGH CARBOHYDRATE-LOW FAT DIETS*

BY JOHN M. FLYNN, M.D.†

IT is admitted by all authorities that diabetics like nondiabetics require proteins, carbohydrates, fats, salts, water and vitamins for carrying on the normal metabolic processes of the body. There is, however, no unanimity of opinion as to the optimum mixture of carbohydrate, protein and fat to be prescribed for meeting part of this requirement. One school (Porges and Adlersberg;[1] Sansum, Blatherwick, and Bowden;[2] Geyelin;[3] and Rabinowitch[4]) favors a high carbohydrate-low fat diet; the other (Newburgh and Marsh;[5] and Petrén[6]) the reverse. The adherents of these opposing schools have endeavored to justify their positions by citing the beneficial results accruing to patients treated by the type of diet they espouse. In the outpatient clinic of the Peter Bent Brigham Hospital we have adhered to the régime of the high carbohydrate-low fat school, not only because of the theoretical considerations brought forth by its adherents, but also because we have found it a practical impossibility to feed high fat-low carbohydrate diets to our ambulatory patients over a long period of time. Patients fed the latter diets tended almost invariably to modify them by increasing the carbohydrate, by decreasing the fat or by doing both.[7] The present paper is written for the purpose of explaining the simplified scheme we have adopted for the calculation of these diets in our outpatient clinic.

Before discussing our dietary scheme it is necessary to say something about the criteria employed to determine the adequacy or inadequacy of a diet prescribed in this disease. These criteria may be obtained from many sources

*From the Medical Clinic of the Peter Bent Brigham Hospital.

†Flynn, John M.—Junior Associate in Medicine, Peter Bent Brigham Hospital. For record and address of author see "This Week's Issue," page 991.

Among the more important of them are the following: the patient's feeling of well-being, his general physical condition, the presence or absence of dehydration, the body weight, the specific gravity of the urine, the twenty-four hour output of urine, glycosuria, ketonuria and blood sugar level.

The simpler criteria of effective treatment are probably overlooked all too frequently in the present era of highly developed laboratory technic. Nevertheless, in our experience with ambulatory cases, it would seem that the patient's feeling of well-being, the study of his general condition by the ordinary office methods and a determination of his body weight yield far more information of interpretable value than many of the laboratory tests employed today. In this connection it seems well to remark that we do not decry laboratory methods of investigating disease but feel that a definite distinction should be drawn between laboratory tests that furnish information of clinical value in the management of patients and those that are chiefly of value in the investigation of disease.

The general physical examination needs no argument to justify its performance in every case of diabetes mellitus. In performing it, it is particularly important to study evidences of dehydration for, as will be shown below, there are many who believe that dehydration is the cause of many of the sequelae of diabetes. The body weight is probably our best quantitative method of determining an individual's nutritional state. As a general rule the optimum weight for a diabetic is one slightly below that termed "ideal" for a normal individual of the same height, age and sex.

The qualitative test for glycosuria, when interpreted in conjunction with other data, is probably our most valuable criterion as to the effectiveness of treatment. Indeed there are many who feel that glycosuria of itself alone entails the series of events that proves so harmful to diabetic patients—glycosuria, polyuria, dehydration, desiccation of the tissues, undernutrition and so forth (Mosenthal;[8] Chang, Harrop and Schaub;[9] Lande;[10] Atchley, Loeb, Dickinson, Benedict and Driscoll;[11] Himwich, Fazikas, Nahum, DuBois, Greenburg and Gilman;[12] Peters, Kydd and Eisenman[13]). In interpreting glycosuria one must always realize that the presence of glucose in a particular specimen of urine does not necessarily indicate that glucose is present in the urine excreted by the kidney at the moment the specimen is passed, but rather that glucose has been excreted by the kidney since the time of the previous urination. One must also distinguish the transient glycosuria of mild degree unaccompanied by polyuria, thirst, dehydration, undernutrition and so forth from the more persistent glycosuria of moderate or severe degree accompanied by the same symptoms. We have generally found it wisest to ignore the former, although we always combat the latter by altering the diet, by exhibiting insulin or by doing both.

Determinations of the blood sugar level seem to us to give information of less practical value in the management of ambulatory patients. While there are some who feel that the blood sugar level should be determined frequently and that every effort should be made to keep this within so-called normal limits, this has seemed to us theoretically unnecessary and practically impossible in cases of this type. Indeed there are those who feel that a high blood sugar when unaccompanied by glycosuria of severe degree is not only not harmful but may even be beneficial (Mosenthal[8]). In ambulatory cases we determine the blood sugar for the purpose of confirming the diagnosis and in cases of arteriosclerosis that are receiving insulin and in which an insulin reaction might be attended by serious consequences.

In view of the foregoing considerations it has been our endeavor to prescribe diets that would subserve the following ends: (1) to maintain the body weight at the optimum level; (2) to avoid glycosuria of such degree as to bring about clinical dehydration; and (3) to secure the patient's feeling of well-being. Wherever the patient does not tolerate a diet that maintains his body weight at the optimum level while he performs the ordinary tasks of life without developing glycosuria of such a degree as to lead to dehydration, insulin is employed as an adjunct to dietary therapy.

Two sheets are used in our scheme for calculating diabetic diets. Sheet 1 is the office record. It contains a list of the various articles of food to be prescribed together with food values for helpings of arbitrary size. These helpings are described in terms of common household measuring utensils on sheet 2. The calculation of the diet is done in the last column on sheet 1 and then the article of food, the number of helpings and any reference to the notes on the second sheet are copied on to the latter. In calculating the diet, the actual carbohydrate, protein, fat and caloric values given on sheet 1 are ignored. Attention is focused chiefly on the glucose equivalent of the different articles of food, determined by the use of Woodyatt's formula,[14] $G = C + .58P + .10F$. An effort is made to give an adequate protein intake and to keep the fat intake as low as possible. To do this the patient is given at least one egg, one moderate helping of meat or fish and one glass of milk, containing approximately 35 grams of protein. Since this is supplemented by the protein contained in bread, in cereals and in vegetables, most of our patients receive between 55 and 75 grams of protein per day. The

fat intake is kept at the irreducible minimum demanded by palatability and by the necessity of feeding fat whenever prescribing protein. It is only when the carbohydrate tolerance has reached high levels, for example, G240, that we allow fat in the form of cream, bacon or mayonnaise. Since butter consumption runs along parallel to that of bread and vegetables, this does not prove too difficult.

The use of this method can be understood more readily by giving an example. Thus we often prescribe a diet of G150 on the initial visit. This is divided into three equal parts of G50, of which one will be eaten at each meal. In this case one might prescribe:

BREAKFAST

	Servings	G	
Egg	1	4	(for protein content)
Fruit No. 1	1	10	
Cereal No. 2	1	13	
½ glass Milk	1	9	(needed with cereal, coffee and so forth)
Uneeda	2	10	
Tsp. Butter	1	1	(for egg, Uneedas and so forth)
Total		47	(Although it was desired to prescribe G50 for the meal, in practice one may take a latitude of G3 above or below this. Thus in the case of a diet of G50 one may prescribe a diet of between G47 and G53)

DINNER

	Servings	G	
Meat or Fish No. 3	1	12	(for protein content)
Vegetables No. 5	2	12	
Fruit No. 1	1	10	
Uneeda	3	15	
Tsp. Butter	1	1	(for Uneedas, vegetables and so forth)
Total		50	

SUPPER

	Servings	G	
1 glass Milk	1	17	(for protein content)
Vegetables No. 5	2	12	
Fruit No. 1	1	10	
Uneeda	2	10	
Tsp. Butter	1	1	(for Uneedas, vegetables and so forth)
Total		50	
Total for day		147	

Commencing with a diet such as this as a basis, the patient's clinical response will determine the direction in which it should be altered and whether or not insulin should be employed as an adjunct to dietary therapy. If the weight decreases below the optimum, one would feel that the diet should be increased. If the weight increases above the optimum or if glycosuria of moderate or severe grade continues, one would feel that the diet should be decreased or that insulin should be employed.

A few self-explanatory notes may be added:

(1) The helping of cereal given in our chart is about one half that which is conventionally eaten at breakfast. As tolerance increases, 2 helpings of cereal, equal to the conventional serving, are prescribed.

(2) Uneedas are useful for adjusting the G value of a diet. They have an equivalent value to other articles of food given in the list. Thus, 2 Uneedas = one helping fruit = one half slice bread; 4 Uneedas = one slice bread = one 3 oz. potato.

(3) The conventional serving of meat or fish weighs approximately 3 ounces.

(4) A medium sized potato weighs approximately 3 ounces.

(5) Every sub-maintenance diet is a high fat diet because the patient supplements his food intake by drawing on the fat depots of his body for maintenance. Hence, a sub-maintenance diet may be a low carbohydrate-high fat diet. According to the school we follow, this results in a lower carbohydrate tolerance than a diet of the opposite type. In confirmation of this we have observed numerous patients who showed glycosuria on a sub-maintenance diet of G150 but who became sugar-free on a diet of G240.

(6) Mid-morning glycosuria may at times be abolished by giving the breakfast fruit in the middle of the morning. The rationale of this seems to lie in the fact that, when one ingests an easily assimilable form of carbohydrate while in the fasting condition, absorption may take place so rapidly that the limits of carbohydrate tolerance, unless these are very high, will be exceeded, thereby leading to hyperglycemia and glycosuria. In this connection we have studied the effect on glucose tolerance of equivalent values of glucose and of Uneedas and have found that the tolerance of the former is much greater than that of the latter. This difference is probably due to variations in the rate of absorption.

(7) Graduated exercise enhances carbohydrate tolerance, particularly in middle-aged diabetics with a low blood pressure.

SUMMARY

This paper is written for the purpose of presenting a simplified scheme for the calculation of diabetic diets of the high carbohydrate-low fat type. Our adherence to this school is motivated not only by the theoretical considerations brought forth by its members, but also because it is a practical impossibility to feed any other type of diet to our patients.

The criteria for judging the adequacy or inadequacy of any diabetic diet are discussed, and emphasis is laid upon the use of the simpler criteria in appraising the condition of patients. Among the more valuable criteria are the general physical examination, especially the study of dehydration, the body weight and the simple qualitative test for glycosuria. The study of

the blood sugar level is considered to be of value only as a diagnostic procedure and as a method of forestalling insulin reactions in arteriosclerotic patients, in whom reactions might prove dangerous.

In our diets the actual carbohydrate protein, fat and caloric values of the foods prescribed are ignored and attention is focused chiefly upon the glucose equivalent, as determined by Woodyatt's formula. Most of our diets are relatively low in protein, although there is some increase parallel to that of carbohydrate owing to the fact that bread and vegetables contain a small amount of protein. Fat is kept down to the limit demanded by palatability, except where the glucose tolerance is relatively high.

SHEET 1 OFFICE RECORD

DIABETIC DIET SHEET

Name..... Date.....

Diet Order. Carb. ..... Pro. ..... Fat..... Calories..... Glucose.....

For Day

C	P	F	Cal.		G	G
4	4	48	464	½ cup Heavy Cream	12	
4	4	24	248	½ cup Light Cream	8	

Breakfast

C	P	F	Cal.		G	G
0	6	6	78	Egg	4	
10	0	0	40	*Fruit No. 1	10	
12	2	0	56	*Cereal No. 2	13	
6	4	4	76	½ glass Milk	9	
5	1	1	26	Uneeda	5	
18	3	0	84	1 slice Bread	20	
0	0	3	27	Tsp. Butter	1	
0	5	15	155	Bacon	5	

Dinner

C	P	F	Cal.		G	G
0	21	9	165	Meat or Fish—3 oz. No. 3	12	
0	28	12	220	Meat or Fish—4 oz. No. 3	17	
4	2	0	24	*Vegetables No. 5	6	
18	3	0	84	Potato—3 oz. No. 4	20	
24	4	0	112	Potato—4 oz. No. 4	26	
10	0	0	40	*Fruit No. 1	10	
5	1	1	26	Uneeda	5	
18	3	0	84	1 slice Bread	20	
0	0	3	27	Tsp. Butter	1	
12	8	8	152	1 glass Milk	17	

Supper

C	P	F	Cal.		G	G
12	8	8	152	1 glass Milk	17	
0	21	9	165	Meat or Fish—3 oz. No. 3	13	
0	6	6	78	Egg	4	
4	2	0	24	*Vegetables No. 5	6	
18	3	0	84	Potato—3 oz. No. 4	20	
10	0	0	40	*Fruit No. 1	10	
5	1	1	26	Uneeda	5	
18	3	0	84	1 slice Bread	21	
0	0	3	27	Tsp. Butter	1	
0	0	15	135	Mayonnaise	2	

*The size of individual helpings is given on sheet 2.

SHEET 2 PATIENT'S COPY

Name..... Date.....

Diet Order. Carb. ..... Pro. ..... Fat..... Calories..... Glucose.....

Diet	
Breakfast	**Amount**
Dinner	
Supper	

1. Fruit—one serving consists of:
   - ½ Grapefruit
   - 1 Orange
   - 10 Strawberries
   - 1 Fresh Peach
   - 1 slice Fresh Pineapple
   - 10 Blackberries
   - ½ Apple
   - ¼ Cantaloupe
   - ½ Banana

2. Cereal—one serving consists of:
   - ½ cup Cornflakes
   - ¼ cup Cooked Cereal
   - ¾ cup Puffed Cereal
   - ½ Shredded Wheat Biscuit

3. Any form of lean meat or fish may be used. One serving consists of 3 oz.

4. An equivalent amount of rice or macaroni may be used.

5. Vegetables—one serving consists of:

2/3 cup of:

Asparagus	Tomatoes
Cucumber	Brussels Sprouts
Rhubarb	Water Cress
Endive	Okra
Sauerkraut	Cauliflower
Beet Greens	Dandelions
Egg Plant	Swiss Chard
Cabbage	Celery
Radishes	Mushrooms
Leeks	Mustard
Artichokes	String Beans (canned)
Spinach	

or 1/3 cup of:

String Beans	Pumpkin
Turnip	Squash
Beets	Carrots
Onions	Green Peas (canned)

Foods as Desired

Lettuce
Clear Broth
Mineral Oil Mayonnaise } see recipe
Bran Wafers }
Tea
Coffee

No sugar or sweets of any kind.
Eat only the foods on this list in the amounts given.

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ARTIFICIAL PNEUMOTHORAX IN ADOLESCENTS

BY RUFUS R. LITTLE, M.D.*

THE results of treatment of pulmonary tuberculosis in the adolescent boy and girl have given rise to the impression that the disease in this age group must be viewed with a great deal of pessimism. It is true that statistics show a higher mortality among young girls and boys than among older individuals. However, articles have been recently published tending to show that artificial pneumothorax will give results in this age group that compare favorably with the results of treatment in older individuals. Brock and Mullen[1] concluded from an investigation of the treatment of patients between 12 and 21 years of age that artificial pneumothorax is by far the method of choice in this age group and, further, that the results of proper treatment show that young women in their 'teens obtain just as good results as do young men in their 'teens and that results of treatment are just as good as they are in older individuals.

The Committee on Artificial Pneumothorax of the American Sanatorium Association has recently made a survey of artificial pneumothorax in representative American tuberculosis sanatoria.[2] Quoting from the conclusions of the committee, "The age of the patient does not, as far as these data show, exert an important influence on the success or failure of pneumothorax therapy. Although the number of cases in the lowest age-group is few, they furnish no substantial support for the common impression that patients under twenty respond poorly. . . . These rather limited data suggest a wider use of therapeutic pneumothorax in the group under twenty, following the indications commonly employed in older patients."

In this present study of the effect of artificial pneumothorax in the treatment of tuberculosis of adolescence, we have assembled a group of 97 cases for consideration. These cases are by no means selected, but simply comprise the first 97 patients treated by pneumothorax in this institution, on whom follow-up notes could be obtained. The end-results of this group cannot as yet be absolutely determined since the great majority of these patients are still receiving collapse therapy. However, in treating these patients we have formed certain definite impressions concerning the effectiveness of this form of therapy. These impressions must of necessity be based upon the clinical condition of the patients as determined by temperature, sputum, weight, blood count and blood sedimentation rate. We are well aware that the clinical appearance of a patient suffering from tuberculosis is often misleading, yet we feel that the course of the disease can be followed with a fair degree of accuracy by very careful observation of the above factors, especially since the collapsed lung makes the x-ray of little value.

As a control group, we have assembled 97 unselected cases receiving routine sanatorium treatment, this group being comprised of the same number of minimal, moderately advanced and far advanced cases as the group in which pneumothorax was attempted.

With very few exceptions the ages of the patients considered in this study ranged between 11 and 16 years, no case being over 16 years on admission. Of the entire group only 4 patients were colored, hence the factor of race cannot be considered.

In the accompanying tables we have grouped the cases first according to sex, then according to classification upon admission, based of course upon the extent of pulmonary involvement. In reviewing these cases we have attempted to correlate the stage of the disease with the possibility of inducing effective pneumothorax and with the prognosis.

Many of these patients have had pneumolyses and in one or two cases there was temporary phrenic nerve paralysis. These procedures were carried out only to increase the effectiveness of the collapse, and their effect on the course of the disease cannot be isolated. Those cases in which thoracoplasty was performed are not included in this study.

Considering first the group in which artificial pneumothorax was attempted we find that there were 63 girls and 34 boys, a ratio of practically 2 to 1. This is in itself a significant fact, for it cannot be doubted that girls in this age group

*Little, Rufus R.—Assistant Physician, North Reading State Sanatorium. For record and address of author see "This Week's Issue," page 991

offer less resistance to invasion by the tubercle bacillus than do boys.

From the statistics of tables 1 and 2 we observe that a successful collapse is most often obtained when the disease is in the minimal stage, both for boys and girls. Collapse was

TABLE 1

GIRLS

	Number	Successful Collapse
Minimal	14	11 — 78%
Mod. Advan.	20	15 — 75%
Far Advan.	29	11 — 38%
Total	63	37 — 59%

TABLE 2

BOYS

	Number	Successful Collapse
Minimal	14	11 — 78%
Mod. Advan.	15	9 — 60%
Far Advan.	5	3 — 60%
Total	34	23 — 68%

considered successful when the conditions outlined by the Committee on Artificial Pneumothorax of the American Sanatorium Association[2] were met, namely:

1. Disappearance of symptoms.
2. Disappearance of bacilli from the sputum.
3. Demonstrable closure of cavities.

TABLE 3

GIRLS

	Successful Collapse	Favorable Prognosis
Minimal	11	10 — 90%
Mod. Advan.	15	9 — 60%
Far Advan.	11	3 — 27%
Total	37	22 — 59%

TABLE 4

BOYS

	Successful Collapse	Favorable Prognosis
Minimal	11	11 —100%
Mod. Advan.	9	7 — 77%
Far Advan.	3	1 — 33%
Total	23	19 — 83%

In tables 3 and 4 the cases in which successful collapse was obtained are considered with regard to the prognosis. It is readily seen that as the disease reaches the advanced stage the prognosis becomes much more grave, even when collapse is successful. From these tables we also see that a favorable prognosis is encountered slightly more frequently in the male group than in the female group.

TABLE 5

GIRLS

Routine Sanatorium Treatment

	Number	Favorable Prognosis
Minimal	14	10 — 71%
Mod. Advan.	20	5 — 25%
Far Advan.	29	1 — 3%
Total	63	16 — 25%

TABLE 6

BOYS

Routine Sanatorium Treatment

	Number	Favorable Prognosis
Minimal	14	8 — 58%
Mod. Advan.	15	8 — 53%
Far Advan.	5	1 — 20%
Total	34	17 — 50%

Considering now the control groups we see in tables 5 and 6 that the prognosis for boys and girls receiving only routine sanatorium treatment is much less favorable than the prognosis for similar groups receiving collapse therapy. It is seen that only 25 per cent of the girls receiving routine sanatorium care may be considered to have a favorable prognosis as compared with 59 per cent of the girls receiving collapse therapy and 50 per cent of the boys without pneumothorax as compared with 83 per cent of the boys with pneumothorax. We again see that the prognosis for boys is more favorable than for girls.

In tables 7 and 8 the combined statistics for boys and girls with successful collapse are compared with the combined statistics for boys and girls receiving only routine sanatorium treatment. It is apparent that successful artificial pneumothorax will increase the incidence of favorable prognosis in each stage of the disease. The percentage of cases with successful collapse in which a favorable prognosis is predicted is exactly double the percentage of cases without collapse.

In all of our cases in which we have been able to induce some degree of collapse of the diseased lung we have noted clinical improvement, as evidenced by lessened symptoms of toxicity, lowered temperature, diminished sputum or some improvement in the patient's general condition which we believe has prolonged life even if a favorable prognosis could not

TABLE 7

BOYS AND GIRLS

With Successful Collapse

	Number	Favorable Prognosis
Minimal	22	21 — 95%
Mod. Advan.	24	16 — 67%
Far Advan.	14	4 — 28%
Total	60	41 — 68%

TABLE 8

BOYS AND GIRLS

Receiving Routine Sanatorium Treatment

	Number	Favorable Prognosis
Minimal	28	18 — 64%
Mod. Advan.	35	13 — 37%
Far Advan.	34	2 — 6%
Total	97	33 — 34%

be predicted. In no instance do we feel that pneumothorax has resulted in an acceleration of the disease process.

CONCLUSIONS

Although we realize that the figures presented are not conclusive, yet we feel that they are definitely indicative of the value of artificial pneumothorax in adolescents. Our results are similar, in most respects, to those published by others. We have been able to arrive at certain conclusions from this study:

1. Sex is an important factor, the female adolescent responding less favorably to collapse therapy than the male adolescent. In this we differ from the conclusions of Brock and Mullen, referred to above.

2. The amount of disease with which an individual is admitted to the sanatorium is the most important factor influencing the prognosis of both sexes, even with effective pneumothorax.

3. Artificial pneumothorax therapy is the method of choice in adolescents.

4. In our series 68 per cent of the patients with effective pneumothorax are at present considered as having a favorable prognosis, while only 34 per cent of a control group of patients of the same age group receiving only routine sanatorium care are classed as having a favorable prognosis.

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MEDICAL PROGRESS

PROGRESS IN HEMATOLOGY*

Late 1934 and 1935

BY WILLIAM DAMESHEK, M.D.†

INTRODUCTION

ADVANCE in hematology continues unabated. The intimate association of the blood cells with almost every conceivable type of bodily disorder is becoming increasingly apparent, making the study of the morphology of the blood in a given case almost imperative. As pointed out in last year's review, hematology has gone a far way from the mere study of the morphology of the blood cells, being now concerned with most of the organs of the body. Thus, a problem in vascular disease of the extremities may resolve itself into a case of polycythemia vera; the occurrence of multiple xanthomata leads the investigator into the study of blood cholesterol and its relation to the reticuloendothelial system; the hypermetabolism of lymphatic leukemia causes speculation on the problem of hypermetabolism in general; and, of course, the importance of the gastrointestinal tract in the pathogenesis of many cases presenting anemia is becoming ever more apparent. Hematology has thus definitely loosened the morphologic shackles which once bound it and has, in response to the times, become increasingly physiologic. It becomes, therefore, more generally apparent that there are in reality no diseases of the blood per se, but rather that various disorders are present in which the blood-forming organs have become implicated.

BLOOD-FORMING ORGANS

Interest in study of the bone-marrow during life has become nothing short of extraordinary. In the past year alone two monographs have been written on sternal puncture: one by Elsa Segerdahl (*Acta med. Scand. Supp.* **59**: 173, 1934), the other by Nils G. Nordenson (*Generalstabens Litografiska Anstalts Forlag Stock-*

*From the Medical Service and Hematology Laboratory, Beth Israel Hospital, Boston. I am indebted to F. A. Davis Co., Philadelphia, publishers of the Cyclopedia of Medicine, for permission to use certain of the material in the Section on Hematology (edited by William Dameshek) of the Revision Service for 1936.

†Dameshek, William—Associate Physician, Beth Israel Hospital. For record and address of author see "This Week's Issue," page 991.

holm, about $4.50). The latter is written in English and has some excellent lithographs. Numerous articles have also been published, some of a general nature and some relating to special investigations. Most of the articles, for example those by Young and Osgood, Reich, and Rohr, have been based on simple puncture of the sternum with a hollow needle followed by aspiration of material with a syringe. It should be remembered that although these puncture methods are simple, they are of only limited value, since they fail to give an idea of the general topography of the bone-marrow. The material obtained is a mixture of blood, fatty and cellular marrow. With the use of Seyfarth's original technic which the reviewer has practiced in about 150 cases (W. Dameshek: *Am. J. M. Sc.* **190:** 617 [Nov.] 1935), a plug of bone (and marrow) is obtained which can be utilized for making sections and "touch" preparations. The resultant cavity can then be curetted and smear preparations made on slides. These are best for studying individual cellular detail; the sections are unsurpassed for study of topography. The smears may at times be misleading, and so may the sections; a combination of the two types of preparations is far better than either alone. The reviewer has found the chief use of the marrow biopsy in the diagnosis of certain cases of chronic anemia and of leukopenia in which the etiology is not readily discernible. Many of these cases have turned out to be examples of aleukemic leukosis. It is frequently impossible to state from a given blood picture, presenting anemia, leukopenia, and thrombocytopenia whether the bone-marrow is "full" (hyperplastic) or "empty" (hypoplastic). In the presence of an arrested maturation, a "full" marrow may be associated with an "empty" blood. The marrow biopsy in these cases is usually helpful. Even with the best of preparations it is sometimes difficult to make a correct interpretation; with puncture preparations in which a small number of marrow cells diluted with a good deal of blood are aspirated, interpretation becomes even harder. If the procedure of sternal biopsy is once considered, it seems to the reviewer that the technic should be as good as one can possibly attain.

With regard to the circulation within the marrow, it is a moot question whether the blood passes through closed capillaries or through sinusoids situated between the parenchymal cells, although most authors are agreed that the circulation is a closed one. W. Gohs (*Virchows Arch. f. path. Anat.* **294:** 103, 1934), on the basis of experimental observations in chickens, criticizes Doan's conception of "intersinusoidal capillaries". He concludes that the bone-marrow contains two types of capillaries, that is, venous and arterial. The venous capillaries he finds are in direct communication with the venous system of the bone-marrow and within them blood formation goes on. The entire system, Gohs concludes, is a completely closed one.

METHODS

Anticoagulants. The subject of anticoagulants is becoming increasingly important because of the rapidly growing use of the hematocrit and the sedimentation rate. T. B. Magath and Margaret Hurn (*Am. J. Clin. Path.* **5:** 548 [Nov.] 1935) analyze the various anticoagulants which have been used and conclude that heparin produces no swelling, crenation, or laking; that dry oxalate causes much shrinkage of erythrocytes necessitating multiplication of the hematocrit value obtained by 1.127; that sodium oxalate in 1.1 per cent solution is suitable and causes no significant swelling or shrinkage. V. G. Heller and H. Paul (*J. Lab. & Clin. Med.* **19:** 777, 1933-34) get around the shrinkage caused by sodium or potassium oxalate by using a mixture of sodium oxalate with ammonium oxalate. If a standard amount is used for say 5 cc. of blood, neither shrinkage nor swelling takes place and no correction factor is necessary. M. M. Wintrobe and J. W. Landsberg (*Am. J. M. Sc.* **189:** 102 [Jan.] 1935) conclude from their investigations that the above mixture of the two types of oxalate is as effective and accurate, in their determinations, as the extremely expensive heparin.

E. M. Greisheimer, Agnes Hodapp, and Edith Goldsworthy (*Am. J. M. Sc.* **190:** 775 [Dec.] 1935) found that sodium citrate is a highly satisfactory anticoagulant (0.5 cc. of a 3 per cent solution for 4.5 cc. of blood). They come to the rather startling conclusion that heparin, often considered the standard anticoagulant, increases the sedimentation rate in all cases.

Sedimentation Rate. In the above-mentioned article, Wintrobe and Landsberg carry out an exhaustive investigation of the sedimentation rate in which such factors as anticoagulant; bore, length, and inclination of the tube; temperature, concentration of the red blood cells are analyzed. These authors, like Rourke and Ernstene working with heparin, found that it was necessary to correct the sedimentation rate for the hematocrit reading, which can conveniently be done in the Wintrobe hematocrit tube. They state it is not essential to make readings every few minutes; by using a correction chart, the reading at the end of an hour may be taken.

It is readily conceded that the sedimentation rate is a relatively "gross" nonspecific test reacting sometimes unpredictably to many conditions. It seems justifiable therefore, except in research investigation, to use (1) a relatively inexact measure, say at the end of an hour,

rather than to go to the trouble of taking readings every few minutes, and (2) some such anticoagulant as ammonium-potassium oxalate or sodium citrate.

CERTAIN CHEMICAL CONSTITUENTS

Hemoglobin. The methods for the estimation of hemoglobin in the blood continue to be as numerous as they are unsatisfactory. The per cent method for recording the amount of hemoglobin continues to be used, despite the great differences in what constitutes 100 per cent. The Sahli method continues to be the most satisfactory clinical method now in use. When properly calibrated against either the Van Slyke O_2 capacity method or an accurate total iron method, and with due attention to the minutiae of technic, an accuracy of ± 3 per cent can be obtained. This is about as good as can be obtained with the more elaborate Newcomer acid hematin method. H. W. Josephs (*Bull. Johns Hopkins Hosp.* **56:** 50 [Jan.] 1935) compared hemoglobin values determined by the Newcomer method and calculated from the iron content in a group of children. There was a high degree of correlation between these two methods in the normal group; under certain abnormal conditions, however, there was more iron in the blood than could be accounted for by the hemoglobin as determined by the Newcomer method. T. G. Klumpp (*J. Clin. Investigation* **14:** 351 [May] 1935) determined the hemoglobin in 57 subjects from estimations of the oxygen capacity and total blood iron and frequently experienced discrepancies which he attributes to the presence of nonhemoglobin iron. For these reasons, he states, it is fruitless to attempt to correlate the values for hemoglobin and oxygen capacity with determinations of total blood iron. This view is in direct contradiction to that of Peters and Van Slyke in their textbook and to the experience of the reviewer since there is, almost invariably, striking correlation between the blood iron and oxygen capacity methods for the determination of hemoglobin. With increasing use of the spectrophotometer or the photometer with various special filters, hemoglobinometry may yet become both simple and accurate. At the present time, it seems best to rely on the Sahli or Newcomer methods for clinical usage and on iron or oxygen capacity methods for research accuracy.

Spectroscopic Methods. There has recently developed a great increase in the use of spectroscopic methods for the detection and measurement of minute quantities of various substances in the blood. The day of the colorimeter seems gradually to be passing and in its place is coming the era of the photometer and spectrophotometer that utilize a given wave-length of light for measurements of intensity of an unknown solution. The spectrograph measures the actual amount of metallic material in a solution by photography of the spectral lines which are formed on ignition. H. Blumberg and T. F. M. Scott (*Bull. Johns Hopkins Hosp.* **56:** 311 [June] 1935) studied the blood lead in clinical lead poisoning and found that about 90 per cent of the lead was carried within the red blood cells, probably in comparatively firm combination. H. Blumberg and T. N. Carey (*J. A. M. A.* **103:** 1521 [Nov. 17] 1934) point out the dangers of the continued use of silver preparations, such as argyrol, and demonstrate the large amounts of silver in the blood of a patient with obscure argyria by means of the spectrograph. These authors suggest the prophylactic use of the spectrographic examination of blood for high and persistent silver content during the use of silver arsphenamine, silver nitrate, mild silver protein, neosilvol, and so forth. Along the same lines are the observations of L. E. Gaul and A. H. Staud (*Arch. Dermat. & Syph.* **30:** 697 [Nov.] 1934; *J. Nerv. & Ment. Dis.* **81:** 265 [Mar.] 1935; *J. A. M. A.* **104:** 1387 [Apr. 20] 1935). These investigators perform "biospectrometric analyses", in which a quantitative spectrographic analysis is made for metallic constituents of an incinerated bit of skin removed at biopsy. By the use of this method, they demonstrated the retention of nickel in psoriasis, lead in cases of workmen coming in contact with lead paints, and of silver following organic and colloidal silver medication.

Porphyrin. Recently a great deal of interest has developed in the porphyrins and in their relation to the metabolism of hemoglobin. The porphyrins are the primary pigments from which are formed such secondary pigments as chlorophyl and hemoglobin. Bilirubin is isomeric with the porphyrins. Fischer studied these substances exhaustively and synthesized them. One of them, coproporphyrin, has been identified by Borst and Königsdörffer (1929) in the megaloblasts of pernicious anemia and the speculation has been made that these cells were laboring under abnormal or deficient living conditions. C. J. Watson (*J. Clin. Investigation* **14:** 116 [Jan.] 1935), who has been one of the few investigators in this country studying this problem, isolated coproporphyrin I from the feces of two typical cases of pernicious anemia. The primary disturbance in this disease may not be in hemoglobin but in its precursor, porphyrin. What relation exists between such widely separated clinical diseases as pernicious anemia and congenital porphyria has yet to be established. In a well studied case of the latter disorder (K. Horsch and C. Carrié, *Ztschr. f. Klin. Med.* **129:** 214, 1935), therapy with liver extract was quite successful in reducing the porphyrin

content of the urine and in ameliorating the many symptoms.

Copper. A. Sachs, V. E. Levine, and A. A. Fabian (*Arch. Int. Med.* **55:** 227 [Feb.] 1935) studied the copper and iron content of the blood in normal subjects. The copper content was about .131 to .132 mg. per 100 cc., whereas the iron content varied from 45 to 50 mg. In anemia, an inverse relation between the blood iron and copper was found, hypercupremia being present when the blood iron was low. The significance of this observation is not yet completely clear although it would seem to indicate that copper therapy would theoretically be of no value in iron deficient states.

BLOOD CELLS

Red Blood Cells. E. E. Osgood (*Arch. Int. Med.* **56:** 849 [Nov.] 1935) continues his careful formulations of normal hematologic standards and presents his results of the study of 500 normal cases. This exhaustive study, although it makes dull reading, is exceedingly valuable from the comparative standpoint. In another paper, E. E. Osgood and R. L. Baker (*Am. J. Dis. Child.* **50:** 343 [Aug.] 1935) present similar studies in normal children of school age and give definitions of what constitutes anemia and polycythemia in children. H. Daum (*Folia haemat.* **53:** 1, 1934) makes a careful study of the various types of basophilic red cells (polychromatophilic cells, reticulocytes and stippled cells). She concludes that all of these cells are substantially identical and that their varying appearances (due to staining and fixing methods) are mostly artefacts. Polychromatophilic red cells and reticulocytes are identical, but the stippled cells probably represent toxically changed immature red cells in which the cytoplasm has undergone a so far undiscovered colloidal change. J. S. P. Beck and C. S. Hertz (*Am. J. Clin. Path.* **5:** 325 [July] 1935) describe a test tube method for demonstration of sickled red cells which consists in fixing the red cells with formaldehyde after they have assumed their characteristic form in a test tube filled with oil. Permanent preparations for classroom or other use may then be made.

Sickling. Although this abnormality of the red cells is undoubtedly more common in the colored race, it is by no means limited to that group. More and more cases are being reported in white people. Thus, D. J. Stephens and A. J. Tatelbaum (*J. Lab. & Clin. Med.* **20:** 375 [Jan.] 1935) report the study of 15 members of an Italian family, 8 of whom exhibited elliptical erythrocytes.

Another inherited characteristic in the red cell is the well-known and extremely important one of "blood group". The 4 blood groups which are utilized in transfusions are of only occasional value in establishing paternity in questionable cases. A. S. Wiener, in collaboration with R. Zinsher and J. Selkowe (J. Immunol. **27:** 431 [Nov.] 1934) continues his work on the agglutinogens M and N discovered in 1927 by Landsteiner and Levine, and with the use of which it is possible to increase the chance for establishing definite knowledge as to paternity in 1 out of 3. The subject of blood groups in all its aspects is fully covered in a recent volume by A. S. Wiener ("Blood Groups and Blood Transfusion," Charles C Thomas, Springfield, Ill., 1935).

White Blood Cells. D. Mainland, B. Du Bilier, and C. B. Stewart (*Canad. M. A. J.* **33:** 667 [Dec.] 1935) and D. Mainland, B. K. Coady, and S. Joseph (*Folia haemat.* **54:** 8, 1935) set out to study the accuracy of differential blood counting and by extremely time-consuming investigations arrived at the conclusion that a good deal of variation existed between successive counts of the same film and duplicate counts of two films taken simultaneously. This is undoubtedly true, but how much practical significance attaches to this observation is doubtful since the blood itself is no exact composition of cells and since no exact inferences should be drawn from a differential count. W. E. Garrey and W. R. Bryan (Physiol. Rev. **15:** 597 [Oct.] 1935) review their careful work on variations in white cell counts and give an excellent review of the literature. Garrey's work has been abundantly confirmed, particularly that relating to the basal leukocyte count. Garrey and Bryan take up such factors as daily variations, posture, random activity, exercise, training, adrenin, digestion, starvation, climate, pregnancy, emotional states, distribution phenomena, and cell life-span. This is an excellent review and should repay careful reading. A. H. Washburn (*Am. J. Dis. Child.* **50:** 413 [Aug.] 1935) continues his standardization of the blood of healthy young infants. These studies are of course extremely important in the appreciation of what constitutes abnormality and are too often disregarded. In normal children, Washburn brings out that the total leukocyte count may vary widely and be subject to great fluctuation, particularly in the lymphocytes. So striking is this fluctuation that it is often unwise to make a conclusion from the study of one blood smear. E. A. Gall (*Am. J. M. Sc.* **191:** 380 [March] 1936) describes a "previously undescribed granule within the lymphocyte". This is a motile, refractile globule normally present in the cytoplasm of 34 per cent of lymphocytes. Its significance is unknown. H. S. Dunning and J. Furth (*Am. J. Path.* **11:** 895 [Nov.] 1935) conclude that microglia of the brain and histiocytes are morphologically and functionally identical and constitute a single cell type. Monocytes may trans-

form into cells indistinguishable from microglia. This observation is of great significance as indicating the functional capacities of the microglia since, if they are truly monocytes, they are then part of the widespread and important reticulo-endothelial system.

That the white cells in the circulating blood continue to be the objects of such intense study would seem to be explained by the relatively recent interest in the monocyte as a third type of blood cell; by the increasing use of the careful differential count of the Arneth-Schilling types, and by the gradual diffusion of the knowledge that the white cells of the circulating blood may (in a very limited way, to be sure) be considered as representing the various blood-forming organs. Reactions of the bone-marrow, the lymphoid system, and the reticulo-endothelial system can to some extent be predicted from the examination of a blood smear.

So many articles (often unduly enthusiastic) have been written on the value of the Arneth-Schilling counts in the study of various infectious diseases that it is refreshing to come across a critical article. C. J. Young (*Brit. M. J.* **2:** 109 [July 20] 1935) observed that the Arneth count sometimes fails to show a "shift to the left" (that is, the presence of immature polymorphonuclears) in acute infections and, conversely, may show the left shift in the absence of infection. He feels that it is necessary to record the various types of cells in their absolute numbers; an absolute increase in the polymorphonuclear output is necessary in the interpretation of a count as evidence of infection. In tuberculosis the differential count has interested many observers. There continues to be discussion regarding the relative value of the sedimentation rate, the monocyte-lymphocyte ratio, and the count of the immature polymorphonuclears. To the reviewer, the type of determination made does not seem to be quite so important as the interest which is taken in the problem. It may be heresy to say this, but it would seem that tuberculosis is still best studied by the temperature chart, the physical findings and the x-ray examination. Occasionally, in every tuberculosis sanatorium, the problem of the value of the above procedures is taken up by an enterprising staff member. With the requisite enthusiasm, fruitful results are obtained. When, as often happens, interest lags, the tests give diminishing returns.

C. H. Smith (*Am. J. Dis. Child.* **49:** 327 [Feb.] 1935) examined the white cells with the supravital technic in 23 patients with the childhood type of tuberculosis. Smith states that the blood count supplies information of a more precise nature of the pathologic process than can be obtained from the complaints of the patient, the physical examination or the x-ray. The monocytes and the monocyte-lymphocyte ratio are the best guides to early manifestations of activity. It may be stated parenthetically that the use of the supravital method in the study of the blood in tuberculosis is often impressive to the onlooker, but how much more information is obtained than by the use of the simple stains is often problematical.

G. Thiele (*Beitr. z. Klin. d. Tuberk.* **86:** 126, 1935) compared the blood picture and the sedimentation rate of the red cells in 100 male patients with open tuberculosis. Although the sedimentation rate was frequently normal, the blood picture always showed considerable alteration, the neutrophils usually showing a shift to the left and the lymphocytes being increased. (The monocytes are not emphasized, as is common in European literature.) The author rejects Schilling's "phases" of "defense" and his interpretation of the hemogram because "they do not correspond to the real conditions". He feels that it is preferable to use Arneth's simplified neutrophil blood picture. G. L. Muller (*New Eng. J. Med.* **211:** 248 [Aug. 9] 1934) did a careful piece of work on the monocyte-lymphocyte ratio in 730 cases of tuberculosis and found a surprisingly close correlation between the ratio and clinical judgment. A high ratio of monocytes to lymphocytes is frequently of grave prognostic import, but may be misleading and may be associated with some such complication as an upper respiratory infection, pleurisy or pneumonia. E. M. Medlar (*Am. Rev. Tuberc.* **31:** 621 [June] 1935) has continued his careful work on the differential count in pulmonary tuberculosis and has even devised a circular slide rule for use in estimating the severity of the infection present and its prognosis.

P. Cohen and S. L. Warren (*J. Clin. Investigation* **14:** 423 [July] 1935) studied the leukocytosis produced by artificial fever. There was a substantial relative and absolute increase in immature polymorphonuclears in 6 of 11 cases with a decrease in lymphocytes, suggesting a mobilization into the circulation of available and nearly mature myeloid cells. (These observations are interesting since the same findings are discovered in fever due to infection.) D. R. Meranze, T. H. Mendell, and T. Meranze (*Am. J. M. Sc.* **189:** 639 [May] 1935) studied the cytoplasmic changes in the neutrophil ("toxic changes") in infections and found that this study often gave more information than does the Arneth-Schilling count. These cytoplasmic changes are of various degrees of intensity ranging from slight irregularity and basophilism of the granules to vacuolization of the cytoplasm. The reviewer agrees with the authors that the polymorphonuclears should be examined closely for evidences of these changes, but would not go so far as to state that no hemogram is complete without the recording of toxic

changes in some quantitative scheme or index. There have been too many indices introduced already into such a nonmathematical tissue as the blood, and their permanent value is doubtful.

BLOOD PLATELETS

These third formed elements deserve more attention than they usually obtain in the routine study of the blood. The chief reason for this is, of course, the relative difficulty in their enumeration. The methods, although numerous, are frequently very time-consuming and often no more accurate than the approximate estimation from the blood smear. The various methods are reviewed by I. Olef (*J. Lab. Clin. Med.* **20:** 416 [Jan.] 1935), who discusses the various types of solution, methods for obtaining and diluting the blood and the relative values of the "direct" and "indirect" methods. He concludes that the "indirect" methods are the most accurate and suggests the use of a modified sodium metaphosphate solution used with a wax mixing cup for preparing proper dilution. In a recent article, R. B. H. Gradwohl (*J. A. M. A.* **105:** 1030 [Sept. 28] 1935) describes a rather involved staining method for the enumeration of the platelets. This seems to the reviewer defective in that, after dilution, the mixture of blood and stain is spread on glass slides, a method which disturbs greatly the fundamental relation of the red blood cells to platelets. The reviewer has had occasion recently (unpublished data) to reexamine his own method (W. Dameshek: *Arch. Int. Med.* **50:** 579 [Oct.] 1932) in which through the use of brilliant cresyl blue, simultaneous platelet and reticulocyte counts may be made. Comparison of this method with several others has again demonstrated that, despite its simplicity, it compares favorably with other more time-consuming methods and is about as accurate as is possible when working with such easily agglutinable bodies as the platelets. The platelets are of importance not only in thrombocytopenic purpura but in the formulation of a complete "index" of bone-marrow activity. Thus, by doing counts of the red cells, leukocytes, reticulocytes, polymorphonuclears and platelets, the extent of bone-marrow activity can be estimated with a fair degree of accuracy.

ANEMIA

Classification. The classification of the various types of anemia according to cell size continues to be widely utilized. To label a case presenting anemia as "primary" or "secondary" is now old-fashioned, since all cases of anemia are secondary to some cause, whether or not this cause is readily demonstrable. It is therefore wise, as pointed out in last year's review, to describe cases of anemia as macrocytic, microcytic or hypochromic, and normocytic. The determination of cell size may be made in 2 ways: (1) The study of the actual size of diameter of the red cell with the micrometer eyepiece or by the use of a diffraction screen apparatus, and (2) the determination of the mean corpuscular volume.

The mean corpuscular volume is obtained by dividing the hematocrit (percentage volume of packed red cells) times 10 by the red cell count in millions. Thus, if the hematocrit is 46 and the red cell count 5.0 million, the mean corpuscular volume is $\frac{46 \times 10}{5.0} = 92$. The resultant figure is expressed in cubic micra.

Normocytic = 84-94 (up to 100 frequently) cu. micra.

Macrocytic = over 100 cu. micra.

Microcytic = under 70 cu. micra.

H. E. Bock (*München. med. Wchnschr.* **81:** 1646 [Oct. 26] 1934) describes results obtained in his study of anemia with the measurement of the red cells by "diffraction micrometry" and finds its chief use in the diagnosis of pernicious anemia. In parenchymal disease of the liver, carcinoma of the stomach, and in certain cases of achylia gastrica, he found that macrocytosis of the red cells was frequently present. R. L. Haden (*J. A. M. A.* **104:** 706 [Mar. 2] 1935) was one of the first to utilize the method of cell-size for classification of the anemias, although his classification is somewhat more complicated. As Haden states, the macrocytic anemias are usually dependent upon a megaloblastic marrow which, in turn, is dependent upon "liver" deficiency. The microcytic or hypochromic anemias are dependent upon iron deficiency (hemoglobin lack). Normocytosis indicates that cells of normal size are being produced by whatever marrow tissue is present (aplastic anemia, and so forth). As pointed out in last year's review, the term macrocytic anemia, and so forth, should be followed by a list, if possible, of the various etiologic agents present. (Thus macrocytic anemia: achylia gastrica, hepatic insufficiency, poor dietary.) This method of classification immediately gives a general idea of the type of anemia present and the various etiologic agents help to give an understanding regarding the underlying physiology. The literature is so replete with terms and names describing not only classifications more or less involved but also specific types of anemia, that any attempt to add a new name should be vigorously opposed. This may be said for the term "achrestic anemia" proposed by J. F. Wilkinson and M. C. G. Israëls (*Brit. M. J.* **1:** 139 [Jan. 26] 1935) for the description of certain cases of macrocytic anemia associated with the presence of free hydrochloric acid in the stomach, the blood picture of pernicious anemia, and

lack of response to liver extract. This type of anemia is thought to be due to failure of utilization, "achrestia", of the antipernicious anemia principle in the liver.

Chronic ("Primary") Hypochromic Anemia. Since there are, strictly speaking, no "primary" anemias, there can in reality not be such a disease as "primary hypochromic anemia". The reviewer introduced this term (W. Dameshek: *Am. J. M. Sc.* **182:** 520 [Oct.] 1931) partly to indicate that some cases of hypochromic (low color index) anemia were just as "primary" as, for example, pernicious anemia; partly to indicate that even pernicious anemia was frequently a "secondary" anemia (poor dietary, gastro-intestinal lesions, and so forth). It is certainly best at the present time to discontinue use of the word "primary" and to use instead the word "chronic". Patients, usually middle-aged women, presenting pallor, sores about the corners of the mouth, wrinkled skin, glossitis, achlorhydria, and hypochromic anemia, are suffering from chronic iron-deficiency which, in turn, is dependent upon such factors as an inadequate dietary, improper functioning of the stomach (achlorhydria, neoplasm) intestinal lesions, chronic occult bleeding, pregnancy, and so forth.

Etiology. The relation of this disorder to various gynecologic abnormalities, particularly menorrhagia, has frequently been stressed. Thus, L. A. Gray and M. M. Wintrobe (*Am. J. Obst. & Gynec.* **31:** 3 [Jan.] 1936) in a study of 40 cases of chronic hypochromic anemia found myomata uteri in 8, endometrial hyperplasia in 5, and unexplained menorrhagia in 14 cases. Furthermore, 12 patients gave a history of repeated pregnancies, postpartum hemorrhage or abortion. Although these figures are undoubtedly significant, it is unfortunate that a control series of women in the same age group were not studied in the same manner.

The association of hypochromic anemia with pregnancy has become well known, and it is likely that the fetus, in its necessity for hemoglobin, abstracts large quantities of the mother's iron store. M. B. Strauss (*Ann. Int. Med.* **9:** 38 [July] 1935) continues his studies on this important subject. Pregnancy, when it occurs in women who are already of the hypochromic type (poor dietary, achlorhydria, and so forth), aggravates the condition strikingly. D. T. Davies and U. Shelley (*Lancet* **2:** 1094 [Nov. 17] 1934) studied 51 apparently normal pregnant women and 20 who had been frankly anemic following their last pregnancy. A normal gastric secretion was found in 45 women who passed through their pregnancies without anemia. Those that had had anemia at a previous pregnancy were found to show either complete achlorhydria or hypochlorhydria, considered to indicate a permanent change in the gastric mucosa. The authors believe that the anemia is due in great part to long-standing gastric anacidity, with resultant inadequate absorption of iron and, therefore, lack of available stored iron for the demands of pregnancy; an inadequate diet is also frequently present.

S. J. Hartfall (*Guy's Hosp. Rep.* **84:** 448 [Oct.] 1934) presents a careful report of the anemia following gastrectomy and gastro-enterostomy. He found that of 91 cases of subtotal gastrectomy and gastro-enterostomy for ulcer, 50 per cent of the women and 16 per cent of the men become anemic, the anemia being usually of the hypochromic type and indistinguishable from that of idiopathic hypochromic anemia. The degree of anemia could be correlated with the amount of gastro-intestinal dysfunction resulting from the operative procedure. This was especially true in the cases in which gastro-enterostomy had been performed with resultant extremely rapid passage of the bolus of food directly into the small bowel. The poor dietary which these patients usually follow was also considered to be a contributory matter by Hartfall. C. W. Heath (*M. Clin. North America* **18:** 1183 [Jan.] 1935) discusses the anemia associated with carcinoma of the stomach and finds that it is usually of the iron-deficiency type. The anemia is explainable on at least 3 different mechanisms: loss of blood, inadequate diet due chiefly to anorexia, and achlorhydria.

Treatment. The efficacy of iron in the treatment of these cases of chronic hypochromic anemia is universally conceded. These patients are suffering from an actual iron starvation which expresses itself in the blood as hypochromic anemia. The actual preparation of iron used and its dosage seem to be passing through certain definite cycles. Thus, for a long time, tiny doses of iron (such as reduced iron 1 grain—0.065 gm. and so forth) were used. Then came the period a few years ago in which emphasis was placed on the necessity for very large dosage. This necessitated the use of 1000 mg. (15 grains) of actual iron, as pointed out by W. Dameshek (*West Virginia M. J.* **30:** 193 [May] 1934), which was obtained from 6 gm. (1½ drams) of ferric ammonium citrate, 1 gm. (15 grains) of reduced iron, and so forth. In the last year or two, the superiority of smaller doses of a soluble ferrous salt, such as ferrous sulfate, has been demonstrated. It is possible that the ferrous salts are better absorbed. C. W. Heath (loc. cit.) uses 0.6 to 1 gm. (10 to 15 grains) of ferrous sulfate daily and C. L. Davis (*M. Clin. North America* **19:** 91 [July] 1935) found as good results from 0.8 gm. (12½ grains) of this salt as had previously been given by 6 gm. (1½ drams) of ferric and ammonium citrate. As pointed out by

Davis (loc. cit.), who gives a review of the various preparations of iron and their relative values, parenteral (injectable) iron is usually of little value because of the small amount of contained iron in the ampoule and, furthermore, because of the necessity for daily dosage. Larger doses if injected cause violent reactions.

The place of copper in the treatment of iron deficiency still remains debatable. C. A. Elvehjem, who has contributed a large number of publications on this point, recently reviewed the entire subject (*Physiol. Rev.* **15:** 471 [July] 1935). Copper is present in all living matter. It appears to be essential in normal hematopoiesis in various laboratory animals, particularly in the rat. Copper alone is of no value, but in animals it appears to be a necessary adjuvant (catalyst?) to the action of iron. Whether it is of value in the treatment of hypochromic anemia in man is questionable, although several observers such as J. C. Hawksley (*Proc. Roy. Soc. Med.* **27:** 1066 [June] 1934) appear to have demonstrated its value in the hypochromic anemias of infancy. S. J. Usher, P. N. MacDermot and E. Lozinski (*Am. J. Dis. Child.* **49:** 642 [Mar.] 1935) report on the prophylaxis of anemia in infancy with iron and copper. The iron was given in the form of ferric glycerophosphate, 0.1 to 0.2 gm. (1½ to 3 grains), daily and the copper in the form of copper sulfate, 0.001 to 0.002 gm. (1/64 to 1/32 grain), daily. The group of infants given both iron and copper not only failed to develop anemia, but also had lower morbidity and mortality rates, particularly following pertussis. The reviewer rarely uses copper and then only in those cases of hypochromic anemia which are unusually refractory to iron therapy. The dose in the adult group is 0.005 gm. (1/12 grain) daily.

PERNICIOUS ANEMIA

Etiology. Recent studies indicate that this prime example of a "primary" anemia is, in reality, a syndrome representing the end-result of the interplay of numerous diverse factors. Chief among these are, besides a possible constitutional and hereditary tendency, the factors of an inadequate dietary, abnormalities in the gastrointestinal tract, and gross disturbance in the liver.

D. K. Miller and C. P. Rhoads (*J. Clin. Investigation* **14:** 153 [Mar.] 1935) present what is undoubtedly the most important experimental contribution to the pathogenesis of pernicious anemia that has yet appeared. These investigators, by feeding dogs a "black-tongue"-producing diet, were able to produce some of the symptoms and signs of both pernicious anemia and sprue; the full-blown picture of pernicious anemia did not, however, develop, nor was there relief with parenteral liver extract. It was concluded that the dog "was not suitable for the production of a pathology identical with that of the human disease". When, however, swine were used as experimental animals and fed a modified Goldberger-Wheeler black-tongue-producing diet, a symptom complex was produced characterized by macrocytic anemia, lesions of the oral mucous membranes, gastric achlorhydria, diarrhea, and motor weakness of the extremities. Not only were these typical clinical manifestations of pernicious anemia present, but the bone-marrow was typically "megaloblastic", the gastric juice showed no trace of Castle's enzyme, and the liver, when extracted and injected, was completely devoid of activity. Furthermore, when potent liver extract was injected into these anemic swine, typical reticulocyte and erythrocyte responses took place. Thus, Miller and Rhoads have been able, by the use of an inadequate diet, to reproduce in an experimental animal the complete picture of pernicious anemia. The nature of the exact inadequacy in the diet must at present remain unsettled. It is apparently not vitamin B_2. Whatever the missing food factor is, however, its first effect when lacking, is an inflammation of mucous membranes, leading, in turn, to atrophy and achlorhydria. Whether these experiments can be wholly applied to man is not yet clear.

Although these experiments of Miller and Rhoads again point to the rather definite possibility that pernicious anemia is somehow concerned with vitamin B deficiency, no exact proof of this has yet been advanced. One has the feeling that somehow vitamin B is concerned, but experimentation at least with animals has thus far been unsatisfactory. It is a curious commentary, that in work with pernicious anemia at least, the swine is closest to the human being in its reactions. Margaret C. L. Gildea, W. B. Castle, E. F. Gildea, and Stanley Cobb (*Am. J. Path.* **11:** 669 [July] 1935) who had maintained for years the relation between vitamin B and pernicious anemia and combined system disease conducted some interesting experiments on dogs. They were able to produce disturbances somewhat similar to those of combined system disease by a vitamin B_1 deficient diet in dogs that were kept from dying by the temporary use of small amounts of vitamin B concentrate.

Castle's concept that the disease is primarily due to a *complete* lack in a gastric enzyme, resulting thereby in a "conditioned deficiency" despite an adequate dietary, has recently been challenged. Thus, S. M. Goldhamer (*Proc. Soc. Exper. Biol. & Med.* **32:** 476 [Dec.] 1934) found that the "intrinsic factor" (Castle's enzyme) was present in cases of pernicious anemia, although reduced in amount. By continuous suc-

tion of the gastric juice in cases of the disease, a sufficient amount was obtained for the trial of Castle's experiment, in which incubation of the juice with meat protein is done, the resultant material being then fed to other patients with the disease. Typical reticulocyte and red cell rises took place, indicating the presence of an "intrinsic factor". C. C. Ungley and G. V. James (*Quart. J. Med.* **3:** 523 [Oct.] 1934) also state that many cases of pernicious anemia, although associated with a histamine-fast achlorhydria, may retain the ability to secrete an intrinsic factor. It is in these cases that yeast is effective, suggesting again the importance of the dietary or "extrinsic" factor.

That certain patients may possess no intrinsic factor and yet not have pernicious anemia is brought out by A. L. Bloomfield and W. S. Polland (*J. Clin. Investigation* **14:** 321 [May] 1935), who cite also the previous work of C. W. Barnett (*Am. J. M. Sc.* **184:** 24 [July] 1932). Bloomfield and Polland followed 43 clinic patients presenting total achlorhydria for several years. In none of these patients, including two in whom "intrinsic factor" had been shown to be absent, did pernicious anemia develop. These investigators feel that "only an occasional person needs the protection of the Castle-Minot antianemic substance to safeguard himself against the disease whatever the ultimate cause of it may turn out to be". Possibly some of the discrepant results may be due to the presence of additional factors in duodenal glands. E. Meulengracht, E. Schiodt and A. S. Ohlsen (*Acta med. Scandinav.* **82:** 352, 375, 384, 1934) studied carefully the antianemic factor in preparations of dried stomach substance from the cardia, fundus, and pylorus, respectively, and then E. Meulengracht demonstrated (*Ugesk. f. laeger* **97:** 725 [July 11] 1935) that the duodenum of swine, like the pyloric portion, possesses a marked antianemic activity. Meulengracht feels that the Brunner's glands of the duodenum are identical with the glands of the pylorus and proposes the term "pylorus gland organ" for the combined groups. These investigations are important as indicating that despite a defective stomach (gastrectomy, and so forth), pernicious anemia may not necessarily develop because of activity of the duodenal glands. T. B. Klumpp and S. Koletsky (Ann. Int. Med. **8:** 991 [Mar.] 1935) and L. G. Zerfas and B. S. Cornell (*Am. J. Digest. Dis. & Nutrition* **1:** 857 [Feb.] 1935) give excellent historical reviews of the relation of the gastric secretion and the diet to hematopoiesis.

A most important article relating to the pathogenesis of pernicious anemia is that on the "Etiology and Treatment of Sprue" by W. B. Castle, C. P. Rhoads, H. A. Lawson, and G. C. Payne (*Arch. Int. Med.* **56:** 627 [Oct.] 1935). This paper is a model of clinical and experimental investigation and will doubtlessly be hereafter referred to as the classical paper on the subject. Sprue and pernicious anemia, these investigators demonstrate, are substantially identical diseases. Minor differences occur, to be sure, but these are no greater than among individual cases. Both diseases are examples of closely related deficiency disease, the chief manifestations consisting in disturbances of the tongue, stomach and intestines, the anemia, and (rarely in sprue) the degenerative lesions of the spinal cord. All the hematologic, gastric, and bone-marrow findings closely corresponded in the two diseases and the clinical manifestations were invariably benefited by adequate doses of parenterally injected liver extract. The inadequate dietary seemed more important in sprue than in pernicious anemia.

M. M. Wintrobe and H. B. Shumacker, Jr. (*J. Clin. Investigation* **14:** 837 [Nov.] 1935) contribute an intriguing paper on the relation of fetal hematopoiesis to the macrocytic anemia of pregnancy and anemia in infants. These authors studied the blood of 12 obviously nonviable human fetuses removed by hysterectomy, together with that of fetuses of rabbits, rats, pigs, dogs and cats. "Anemia" was always present in the fetus, gradually diminishing in severity as the fetus matured. The anemia was of the macrocytic variety, with extremely high mean corpuscular volumes and mean red cell diameters. The rising values in the red blood count with increasing maturity of the fetus was strikingly similar to the rising erythrocyte level with specific therapy in pernicious anemia. These observations bring up many interesting speculations: that the fetus suffers from a "liver deficient" state which gradually becomes ameliorated as "liver substance" is removed from the mother; that in certain instances, the mother's store of liver substance may become so depleted that she herself will develop pernicious anemia; and that the very grave anemia of the newborn known as erythroblastosis fetalis may be due to "liver deficiency". (The latter observation has been questioned.) J. F. Wilkinson and M. C. G. Israëls (*Brit. M. J.* **1:** 139 [Jan. 26] 1935) conceive that in certain cases of apparent pernicious anemia which do not respond to liver extract there may be an actual inability to *utilize* liver (*achrestia* —achrestic anemia). This is an attractive hypothesis which may be of service (at present) in explaining the refractoriness to therapy of certain cases of pernicious anemia.

Much interest has recently been stimulated by the insistence of various authors in the identity of the macrocytic anemia associated with certain cases of hepatic disease with pernicious anemia (S. M. Goldhamer, R. Isaacs, and C. C. Sturgis [*Am. J. M. Sc.* **188:** 193 (Aug.) 1934];

M. M. Wintrobe and H. B. Shumacker, Jr. (*Arch. Int. Med.* **57:** 289 [Feb.] 1936). The comments of Minot and Castle in the *1935 Year Book of General Medicine* regarding this important subject should be read by those interested. They make this cogent observation: "Since macrocytosis is common to the anemias of leukemia, Hodgkin's disease, aplastic anemia, benzol poisoning, and other anemias seemingly unrelated to pernicious anemia, it is scarcely to be expected that deficiency of liver extract will be found in all instances of pernicious anemia. The clinical evidence and the logic are equally in favor of the macrocytic anemia of such patients as having no dependence on deficiency of liver extract."

Treatment. Aside from etiologic considerations, most of the articles about pernicious anemia are concerned with therapy. A completely satisfactory method for the assay of various antianemic substances has not yet been discovered, despite some interesting observations regarding the reticulocyte responses which occur in guinea pigs. B. M. Jacobson (*J. Clin. Investigation* **13:** 714 [July] 1934 and **14:** 665 [Sept.] 1935) may be said to have created a mild sensation when he announced what was apparently the long sought for solution for an animal assay method for liver extract. This involved the use of guinea pigs which were "reactive" in the sense of a reticulocyte rise occurring after the administration intraperitoneally of a preparation of liver extract. In these reactive animals, a reticulocyte count of 2 per cent or over occurring for 2 days within 6 days after the administration of a test material indicated a positive response; a negative response was present with a reticulocyte count of 1.8 per cent or under in the same period. Not only did this investigator maintain that the reticulocyte response in guinea pigs was a specific one (dependent upon a "liver deficient state in normal guinea pigs") but he went farther and defined a unit of hematopoietic activity ("guinea pig unit") with which he was able to assay quantitatively various substances including the "intrinsic" and "extrinsic" factors of Castle. Jacobson's work was soon confirmed by D. K. Miller and C. P. Rhoads (*New Eng. J. Med.* **213:** 99 [July 18] 1935) who stated that "it must be shown clearly that the induction of the reticulocyte response depends upon the same pathologic mechanism as that which obtains in the human being with pernicious anemia." Miller and Rhoads concluded that their experiments satisfactorily demonstrated this relation. It is well, however, to await the test of time before accepting this method as proved.*

*In an article published in 1936 by L. S. Goodman, A. J. Geiger, and T. G. Klumpp (J. Clin. Investigation **15**:435 [July] 1936) there is this footnote from a personal communication by Miller and Rhoads, "Further experimentation has advanced incontrovertible evidence that guinea pig reticulocytes may increase to a level of over 2 per cent from a variety of causes unassociated with the administration of substances effective in the treatment of pernicious anemia. Experiments are under way in an attempt to elucidate the cause of spontaneous variations in numbers of reticulocytes; such spontaneous variations demand that the greatest care be used in employing the guinea pig as a test for anti-anemic substances." The article referred to of Goodman, Geiger, and Klumpp would seem on its face to dispose effectively of Jacobson's method. A large and well-arranged series of experiments is presented which inevitably lead to the following conclusion, "The normal adult guinea pig shows considerable and unpredictable spontaneous fluctuations in reticulocyte levels. These variations are of such a nature as to render this normal animal unsuitable for assaying the potency of materials effective in pernicious anemia."

The human assay of liver extract remains our only completely satisfactory one and this is beset with many difficulties which are discussed by W. Dameshek and W. B. Castle (*J. A. M. A.* **103:** 802 [Sept. 15] 1934). These authors criticized the then current methods of labeling liver extracts and concluded that, in the refinement of the various extracts, potent material is lost to greater or less extent. (The Council on Pharmacy and Chemistry of the American Medical Association has taken cognizance of this and other work and has established [*J. A. M. A.* **105:** 1269 (Oct. 19) 1935] new requirements for the acceptance of liver and stomach preparations.)

Efforts to isolate the antianemic principle in liver continue apace. B. Strandell (*Nord. med. tidskr.* **10:** 1217 [Aug. 3] 1935) by an as yet secret method has been able to derive from 100 gm. of liver from 1 to 27 mg. of material which is therapeutically effective. H. D. Dakin and R. West (*J. Biol. Chem.* **109:** 489 [May] 1935) have isolated a product from liver extract effective in very small dosage and which contains at least 6 amino acids. Y. Subbarow, B. M. Jacobson, and C. H. Fiske (*New Eng. J. Med.* **212:** 663 [April 11] 1935) isolated from liver extract 2 substances both effective in guinea pigs. Fraction "A" which was apparently 1-tyrosine contained 16,700,000 guinea pig units per gram of material. Fraction "C" which assayed 10,660,000 guinea pig units was apparently a complex purine such as is found in the wings of certain yellow butterflies. It should be noted that the work of Dakin and West and of Subbarow, Jacobson and Fiske seems to be mutually contradictable. The potency of the Dakin and West material has recently been investigated abroad by C. C. Ungley, L. S. P. Davidson and E. J. Wayne (*Lancet* **1:** 349 [Feb. 15] 1936) and found to be quite active. Subbarow, Jacobson, and Fiske's assays on human subjects have not yet been published.

Aside from these rather theoretical observations, the search for the most effective and the most conveniently used antipernicious anemia substance continues unabated. The development of liver therapy has been traced by G. R. Minot (*Lancet* **1:** 361 [Feb. 16] 1935) in his Nobel Prize lecture. It is an interesting commentary that when an injectable substance such as insulin is introduced, the medical public clamors for an

oral preparation and then when an oral preparation such as liver extract is discovered, the cry is for an injectable material. Now we have dry powdered liver extract, dry gastric extract, dry liver extract activated by gastric extract ("extralin"), liquid oral liver extract (both alcoholic and nonalcoholic), and a large number of assorted types of injectable liver extract. It is no wonder that the practitioner is sometimes bewildered by the wealth of material at his command and by the conflicting claims of rival manufacturers. It may be stated here that some few patients, chiefly those without neurologic involvement, may be well maintained on one of the oral extracts whether dry or liquid. Others, and especially those in whom neurologic symptoms are prominent, require frequent injections of a potent parenteral extract. This is given daily, twice weekly, weekly or biweekly depending upon the type and severity of the case at hand. The reviewer is accustomed to use a so-called "concentrated" extract given usually weekly or biweekly and at times supplemented either by liver itself or by some form of oral liver extract. One should not be misled at the present writing by the attractive promises of potency inherent in extreme concentration. Several observations have recently been made indicating that prolonged and intensive therapy with parenteral therapy is effective in the treatment of the neurologic lesions of pernicious anemia (R. F. Farquharson, *Canad. M. A. J.* **33:** 473 [Nov.] 1935; M. B. Strauss, P. Solomon, A. J. Schneider, and A. J. Patek, Jr., *J. A. M. A.* **104:** 1587 [May 4] 1935).

Liver therapy is of value not only in pernicious anemia proper but in all conditions in which "liver deficiency" is present, even when the cause (such as pregnancy, fish tape worm, poor dietary) is readily apparent. Thus W. B. Castle, C. P. Rhoads, H. A. Lawson and G. C. Payne (*Arch. Int. Med.* **56:** 627 [Oct.] 1935) report the remarkable effects in sprue.

Recently, a peculiar, shall we say, atavism, came into being, namely the idea that pernicious anemia is a "toxic" state, to be treated by a detoxifying agent, that is, Congo red. This idea was promulgated by M. Massa and G. Zolezzi (*Klin. Wchnschr.* **14:** 235 [Feb. 16] 1935) who described the results of the injection of a 1 per cent solution of Congo red intravenously in 14 cases. Careful review of their cases will show that the favorable results are usually greatly delayed in their inception and frequently helped along by liver or other antianemic substances. More recently, their work is said to have been confirmed by C. Mermod and W. Dock (*Science* **82:** 155 [Aug. 16] 1935) who treated two cases in similar fashion. They were also able to obtain rises in guinea pig reticulocytes with the dye. What, if any, rationale there is to the procedure is as yet a mystery. Two cases of the reviewer's relapsed to very low levels when given Congo red. It is no great prophecy to foretell that this new treatment is doomed to an early demise.

The therapeutic effects of vitamin B in pernicious anemia continue to be studied. D. K. Miller and C. P. Rhoads (*New Eng. J. Med.* **211:** 921 [Nov. 15] 1934) first fed mixtures of gastric juice incubated with vitamin B_1 containing substances to patients with pernicious anemia and failed to obtain responses. However, when egg white (containing vitamin B_2) and gastric juice mixtures were fed to the same patients, sharp increases in reticulocytes took place. Despite this striking experimental evidence, Miller and Rhoads are unwilling to conclude that vitamin B_2 and the antipernicious anemia factor are identical. This must await isolation of the vitamin in pure form. C. C. Ungley and G. V. James (*Quart. J. Med.* **3:** 523 [Oct.] 1934) did some interesting experiments with various vitamin B concentrates and yeast autolysates in human pernicious anemia and at times, especially when "Mannite" was used, obtained fairly satisfactory therapeutic results. This was especially true in those cases distinguished by a deficient dietary. H. C. A. Lassen and H. K. Lassen (*Am. J. M. Sc.* **188:** 461 [Oct.] 1934) in their experiments with various fractions of vitamin B showed pretty conclusively that neither vitamin B_1 nor vitamin B_2 had any antianemic effect in cases of pernicious anemia and that these substances were therefore not the "extrinsic" substance. Is it not possible that various investigators are working with different cases of pernicious anemia? Not every case of macrocytic anemia is brought about in the same way. Some cases undoubtedly react to a good diet or to a high vitamin B diet; perhaps these have had a deficient diet. Those cases which do not might have developed the pernicious anemia "complex" through some other mechanism.

Other Types of Anemia

When we finish with the description of chronic hypochromic anemia and the pernicious anemia group, there is left a small number of conditions in which, although anemia is an outstanding feature, there is neither evidence of iron deficiency nor liver deficiency. The practitioner may discover this as frequently happens, when a given case fails to respond both to liver and iron. Or it may be suspected when the anemia is of the normocytic or somewhat macrocytic type, and associated with very low leukocyte and platelet counts. In these cases of obscure anemia, conditions of marrow destruction must be considered: "aleukemic" leukemia with marrow replacement, lymphosarcoma or other malignant tumor metastasizing widely into the

marrow spaces, aplasia of the marrow as the result of a poison such as benzol, radioactive substances, gold and so forth. The diagnosis is often extremely difficult in these cases and requires very careful study. In the reviewer's hands bone-marrow biopsy has proved of greatest value in just these cases.

Aplastic Anemia. Under the heading of "marrow insufficiency" W. S. Middleton and O. O. Meyer (*Ann. Int. Med.* **8:** 1575 [June] 1935) report several cases of aplastic anemia which they feel represent complete failure of bone-marrow growth with resultant anemia, leukopenia, and thrombocytopenia. This failure of the bone-marrow in toto may be "selective" in character, only the red cells, the white cells or the platelets being affected. If the platelets alone are affected, thrombocytopenic purpura results; if the leukocytes alone are involved, agranulocytosis develops. This is beautifully illustrated in cases of poisoning with gold salts and with arsphenamine, in certain cases anemia, in certain cases thrombocytopenia, in others leukopenia being present. Middleton and Meyer (loc. cit.) suggest that these entities of aplastic anemia, thrombocytopenic purpura and agranulocytosis are interrelated diseases. Newly discovered etiologic agents active in the causation of aplastic anemia are constantly being found. Thus, C. W. Baldridge (*Am. J. M. Sc.* **189:** 759 [June] 1935) describes a group of 3 cases of macrocytic anemia following the use of hair dye; the first of these cases was typical in all its features of aplastic anemia. Many hair dyes contain various aniline derivatives and are therefore potentially dangerous.

As regards treatment, no advance has been made. Transfusions are given until the patient shows evidences of recovery or until the condition seems hopeless. Liver extract, pentnucleotide, iron, and so forth, seem to be of no value. C. A. Doan (*Cyclopedia of Medicine*, Revision Service, 1936) suggests splenectomy in selected cases.

"Splenic Anemia." As stated in previous reviews, the term splenic anemia means very little and is more often a hindrance rather than a help in diagnosis and treatment. There is literally a host of conditions in which, together with splenic enlargement, anemia is present. In fact, it is decidedly unusual to have splenic enlargement without some degree of anemia. The term "splenic anemia" has therefore been applied to about every condition in which splenomegaly is present: typhoid fever, malaria, syphilis of the spleen and liver, chronic infectious processes especially in children, cirrhosis of the liver, amyloidosis, Gaucher's disease, myelogenous leukemia, Hodgkin's disease, lymphosarcoma, and so forth. That there is a condition distinct from cirrhosis of the liver, primary in the spleen, characterized by splenomegaly, anemia, leukopenia and without etiologic background is seriously open to question, despite the popularity of the now synonymous terms splenic anemia and Banti's disease. The late Ralph C. Larrabee* (*Am. J. M. Sc.* **188:** 745 [Dec.] 1934) analyzed 47 cases which most people might have called Banti's disease and in which an etiologic factor was not readily discernible. In 14 of these cases, the etiologic factor was never discovered; in the other 33, the following factors were discovered: alcoholic cirrhosis, toxic cirrhosis, syphilitic cirrhosis, other types of cirrhosis, hepatic abnormalities not cirrhosis, adhesions, congenital heart, ptosis of the spleen. In about one-half the cases, cirrhosis of the liver was present and the splenomegaly in most if not all was due to various lesions interfering with the outflow of blood from the spleen. The changes in the spleen were interpreted by the pathologist (F. B. Mallory) to be due to long-continued passive congestion.

In an exceedingly interesting presentation of a case record (Case Records of the Massachusetts General Hospital: *New Eng. J. Med.* **213:** 373 [Aug. 22] 1935) participated in by an internist, a pediatrician, a surgeon, and the pathologist, the subject of splenic vein thrombosis is discussed from various angles. Banti, in his original articles on splenic anemia, undoubtedly included a variety of different disorders in which such similar features as splenomegaly, hepatic cirrhosis, anemia, and leukopenia were present. In recent years, the importance of splenic vein thrombosis has been recognized as the initial factor in certain cases of splenomegaly characterized by hematemesis without involvement of the liver in a cirrhotic process. The hematemesis may be due to secondary engorgement in the portal circulation, with resultant involvement of esophageal veins, or to dilation with rupture of the vasa brevia of the stomach. These cases tend to occur chiefly in children (R. M. Smith and P. J. Howard: *Am. J. Dis. Child.* **34:** 585 [Oct.] 1927) and splenectomy, although of temporary value, does not result in cure, since other thromboses in the portal circulation usually result and the patients almost invariably die of repeated hematemesis. H. D. Leinoff (*Ann. Int. Med.* **9:** 85 [July] 1935) presents a case of this type illustrating the difficulties in diagnosis. The patient described was operated upon 5 times before the real diagnosis became apparent and splenectomy was done with relief. Before making a diagnosis of so-called splenic anemia, it behooves the physician to rule out all the possible causes of splenomegaly, associated with

*Dr. Larrabee died in 1935. He was primarily a clinician and was distinguished by his sound, often homely judgment in "blood" conditions. He was one of the first American physicians to become interested in abnormalities of the blood-forming organs, and organized the first "Blood Laboratory" and "Blood Service" in Boston at the City Hospital.

anemia. Chief among these are aleukemic leukosis, luetic splenohepatomegaly, chronic malarial spleen, cirrhosis of the liver, Hodgkin's disease, congenital hemolytic anemia, and so forth. Occasionally, after numerous diagnostic procedures are accomplished, there is left a case in which is present unexplained splenomegaly, leukopenia, slight anemia and, frequently, hematemesis. The diagnosis of Banti's disease may then be considered. R. W. B. Ellis (*Practitioner* **134:** 317 [Mar.] 1935) states that in a child with splenomegaly and anemia, there must be ruled out the presence of a generalized infection such as syphilis, tuberculosis or a subacute streptococcic infection. Malaria and kala-azar should be considered. D. O. Wright (*Ann. Int. Med.* **8:** 814 [Jan.] 1935) points out that a macrocytic anemia may occur in Banti's disease when portal cirrhosis is present. This may be linked up with the macrocytic anemia of cirrhosis of the liver, as described by Goldhamer. Wright states that the concept that Banti's disease is always accompanied by a microcytic type of anemia is erroneous.

Splenectomy in cases of "chronic congestive splenomegaly" (to use Larrabee's term, which seems a good one) was discussed at length at a symposium on splenectomy held at the 1935 meeting of the American Medical Association. C. A. Doan, G. M. Curtis, and B. K. Wiseman (*J. A. M. A.* **105:** 1567 [Nov. 16] 1935) although noting the dangers inherent in the operation in late stages of the disorder, made a plea for the operation in early cases. They felt that splenectomy might either delay or even prevent the progress of the disease. It it difficult, as brought out in the discussion of this paper, to bring oneself to splenectomy in an early case, in which diagnosis is so difficult; again, it is well known that many cases survive for 5 to 20 years after an initial hematemesis from esophageal or gastric varices in which nothing has been done. The statistics for splenectomized and nonsplenectomized cases in a comparable series would probably show very little difference, and might be in favor of the nonsplenectomized group (which has not suffered the hazards of the operation).

Hemolytic Anemias. It is customary to combine under this group not only congenital and acquired hemolytic jaundice, but erythroblastic (Cooley's) anemia, and sickle cell anemia, although it is recognized that the hemolytic factor in the latter 2 conditions may be slight.

As pointed out in last year's review, the greatest advance recently made in *Congenital Hemolytic Anemia* is the recognition that the most important feature of the disorder is an abnormality of the red cells which are smaller and more spherical than normal and thus more ready to burst (R. L. Haden, *Am. J. M. Sc.* **188:** 441 [Oct.] 1934). This is brought out in vitro by the fragility test in which the red cells come in contact with hypotonic solutions of salt. The spherical character of the cells is brought out not only by direct study but by comparison of the percentage volume of packed red cells with the red cell diameter. The cell diameter in these cases is diminished, often greatly so and yet the hematocrit may be normal or even increased. This can be due only to an increased thickness of the red cell which is a fundamental abnormality. Other associated abnormalities were studied by K. Hansen and E. Klein in a large family with the disorder (*Deutsches Arch. f. klin. Med.* **176:** 567, 1934): tower skull, broad root of the nose, numerous abnormalities of the eyes, bilateral mongolian fold, carious dental abnormalities, and so forth. H. Lehndorff (*Med. Klin.* **31:** 74 [Jan. 18] 1935) presents an important article on the nature of congenital hemolytic disease which he calls "spherocytic disease". Lehndorff states that this congenital disease may remain latent for a long time, but its manifestation may be brought on by such factors as infection, exposure, or overexertion. When fully developed, 3 characteristic symptoms are present: icterus, pallor, and splenomegaly; and 3 hematologic signs: microcytosis, increased fragility of the red cells and increase in reticulocytes. Microcytosis is most striking, and the red cells are spherical and therefore have a greater volume than the normal erythrocytes. These spherical red cells being more fragile than normal, tend to be broken down more readily by the reticuloendothelial system and therefore the spleen enlarges. Lehndorff feels that the nature of the disease is best explained by assuming a congenital abnormality of the erythropoietic system with the production of spherical rather than disc-shaped red cells. He feels that the treatment should be consistently palliative (liver, iron, transfusion) unless hemolytic crises supervene, when splenectomy is indicated. C. A. Doan, B. K. Wiseman, and L. A. Erf (*Ohio State M. J.* **30:** 493 [Aug.] 1934) and C. A. Doan, G. M. Curtis, and B. K. Wiseman (*J. A. M. A.* **105:** 1567 [Nov. 16] 1935) point out the striking results which occur with splenectomy in these cases. It is in this disease that the operation of splenectomy is most strikingly successful and productive of a permanent cure. The Ohio State group has done emergency splenectomies in individuals with "hemoclastic crisis" and this has often resulted in a sudden spectacular release of red cells following ligation of the splenic pedicle while the patient is still on the operating table. Doan and his associates make much of a hypothetical "hemolytopoietic equilibrium" which exists between the blood-forming and blood-destroying organs and are inclined to un-

derestimate the importance of the abnormality of the red cells as shown by others.

An occasional article is written on an unusual type of hemolytic anemia apparently infectious in origin and first described by Lederer in 1925 and Brill in 1926. The disorder is also well described in a case report by F. Corelli (*Haematologica* **17**: 141, 1936) and is characterized by acute onset with high fever, dyspnea, extreme asthenia, icterus, macrocytic anemia, leukocytosis, normoblastosis, and favorable prognosis with transfusions and liver extract.

Erythroblastic (Cooley's) Anemia. There has been no definite advance in the delineation of this disease which, like congenital hemolytic icterus, is characterized by excessive blood destruction in association with increased blood formation. The latter is frequently so striking that the enlarged marrow spaces result in defects (striae) of the skull visible by x-ray. There is at least one important difference, however: splenectomy is of no value in Cooley's anemia. D. H. Kelly and L. F. Hill (*J. Iowa M. Soc.* **25**: 9 [Jan.] 1935) summarize the findings in this disease: constant racial (Mediterranean peoples) and familial incidence, mongoloid facies, many nucleated red cells in the peripheral blood, splenomegaly, changes in the bones. H. W. Josephs (*Internat. Clin.* **2**: 139 [June] 1935) groups erythroblastic anemia, sickle cell anemia, and congenital hemolytic anemia together since they not only have definitely constitutional factors, but all have somewhat similar blood pictures dependent upon the interaction of (1) hemolysis, (2) compensatory regeneration, and (3) a tendency on the part of the blood-forming tissue to produce immature forms. A somewhat similar line of reasoning is espoused by H. Lehndorff (*Schweiz. med. Wchnschr.* **65**: 333 [April 13] 1935) who classifies under the term "erythroblastic disease" the following: fetal erythroblastoses, congenital hemolytic jaundice, Cooley's anemia, and even the almost defunct von Jaksch anemia. He takes the rather extreme view that the erythroblasts present in these cases are evidences, not of excessive bone-marrow activity, but are abnormal blood cells, abnormally found in the marrow and of no value as oxygen carriers in the blood.

Sickle Cell Anemia. C. S. Ryerson and K. L. Terplan (*Folia haemat.* **53**: 353, 1935) report two unusual cases in which careful autopsies (all too few in the disease) were done. In one rather acute case, the extreme degree of anemia seemed to be directly responsible for death; in the other case, there was severe degeneration of the liver. Attention is again directed to the extremely small size of the spleen often present in these cases: 2 gm. in one case.

Anemia in Children. The same etiologic factors are present in the anemias of infancy and childhood as are present in adult cases of anemia. These are well described by L. G. Parsons and W. C. Smallwood (*Practitioner* **134**: 298 [March] 1935). There are, however, a few abnormalities inherent to infancy. H. W. Josephs (*Bull. Johns Hopkins Hosp.* **55**: 335 [Nov.] 1934) studied the physiologic anemia developing in normal infants during the first two months of life. This he found was due mainly to increased blood destruction, although this phenomenon did not wholly account for the anemia. *Erythroblastosis fetalis* or *icterus gravis neonatorum* has been well described recently, among others, by L. G. Parsons and W. C. Smallwood (*Practitioner* **134**: 298, 1935). This occurs in newborn infants and is characterized by intense jaundice, a blood picture resembling the bone-marrow in the large variety of all types of cells present, and occasionally degenerative lesions in the brain ("kernikterus"). The cause of the condition is unknown but it seems to be a congenital defect of the blood-forming organs. Judiciously given transfusions repeated frequently have proved life-saving in many instances (L. K. Diamond, Personal communication). H. M. Zimmerman and H. Yannet (*Am. J. Dis. Child.* **49**: 418 [Feb.] 1935) describe the cerebral manifestations of the disease which are characterized by mental retardation, spasticity, athetosis, convulsions, and emotional instability. These changes are apparently due to involvement of the basal ganglia by the intense jaundice.

Nutritional Anemia. Parsons and Smallwood and J. C. Hawksley, R. Lightwood, and U. M. Bailey (*Arch. Dis. Childhood* **9**: 359 [Dec.] 1934) describe the "milk anemia" of infants which in many respects is similar to the chronic hypochromic anemia of adults, and dependent upon the low iron content of a milk diet too long persisted in. In treating the iron deficiency anemia of children, the following preparations are useful: reduced iron, 1 grain t.i.d. mixed with 2-3 times its weight of sugar; elixir or syrup of ferrous sulfate. Too much has been said about the use of copper in infants. The reviewer feels that this drug is too dangerous for indiscriminate use even in infants.

HEMORRHAGIC DISORDERS

W. H. Howell, one of the pioneer workers on coagulation of blood, writes an excellent review of the theories of blood coagulation (*Physiol. Rev.* **15**: 435 [July] 1935), with particular reference to the literature appearing since 1929. He deplores the enormous number of facts which have been adduced and the lack of uniformity of conclusion derived from these facts. The theory of Morawitz is still main-

tained although the essentials of the theory and the manner of its workings are the subjects of much discussion. This theory contends that thrombin is formed from precursors (prothrombin, calcium, a tissue factor). In the presence of thrombin, fibrinogen is converted to fibrin. A factor inhibiting coagulation may also be present in the circulating blood.

Hemophilia. Etiology. Much continues to be written about this mysterious hereditary disease. R. P. Custer and E. B. Krumbhaar (*Am. J. M. Sc.* **189:** 620 [May] 1935) describe the histopathology of the bone-marrow in hemophilia, rightly regarded by them as "an unexplored field". The red and white cells of the marrow in their 3 cases were within normal limits but the thrombocyte series was definitely abnormal in that younger forms of megakaryoblasts were present in increased numbers together with an increased number of megakaryocytes. This, the authors felt, indicated a relation of the blood platelets to the hemophilic process. A. J. Quick, M. Stanley-Brown, and F. W. Bancroft (*Ibid.* **190:** 501 [Oct.] 1935) studied the coagulation defect in the disease. They state that only 4 constituents are essential for clotting: prothrombin, thromboplastin, calcium, and fibrinogen. It should theoretically be possible to determine which of these constituents is at fault. Previous studies have demonstrated that there is probably no defect in the thromboplastin, fibrinogen, or calcium. The above authors failed to find, however, any defect in the fourth factor, prothrombin, despite their development of a new test. The mystery of why hemophilic blood does not clot must still remain obscure.* R. S. Handley and A. M. Nussbrecher (*Quart. J. Med.* **4:** 165 [Apr.] 1935) present 3 cases of hereditary bleeding in women, in which all the features of hemophilia were present. Whether "pseudohemophilia" was present or whether these cases were examples of true hemophilia in homozygous females is debatable.

Treatment. Completely negative results continue to be obtained with the administration of various types of female sex hormone in the treatment of hemophilia. Thus, what seemed to be a spectacular advance in the treatment of this disease has proved a fiasco. These negative results are discussed in a careful study by W. B. Chew, R. P. Stetson, G. V. Smith, and O. W. Smith (*Arch. Int. Med.* **55:** 431 [Mar.] 1935), who found, however, a possible adverse factor to blood clotting in hemophilia in a gonad-stimulating hormone of the anterior pituitary gland. Single case reports continue to give what purport to be good results in severe cases of hemophilia, viz., the case of K. Franke and S. Litzner (*Med. Klin.* **31:** 520 [Apr. 18] 1935). These authors gave 100 units of an ovarian hormone preparation intravenously to a desperately ill patient with good results. H. W. Jones and L. M. Tocantins (*J. A. M. A.* **103:** 1671 [Dec. 1] 1934) discuss the various methods of treatment in hemophilia and conclude that the intravenous transfusion of unmodified blood constitutes the best method for the prevention and treatment of acute attacks of bleeding; citrated blood, they feel, causes more frequent reactions. Intramuscular injection of 20 cc. of whole blood has appeared to benefit some patients. Fresh serum is a satisfactory local hemostatic agent. As regards other methods of treatment, S. M. Peck and N. Rosenthal (*J. A. M. A.* **104:** 1066 [Mar. 30] 1935) found that moccasin snake venom was of no value in 3 cases of hemophilia. O. Riesser (*Klin. Wchnschr.* **14:** 958 [July 6] 1935) found that apple pectins reduced the clotting time of normal rabbit's blood and suggested their use in human beings. C. P. Waldorp and A. G. Alvarez (*Semana méd.* **1:** 6 [Jan. 3] 1935) tried to reduce the clotting time in their cases of hemophilia by aolan, calcium chloride, 30 per cent sodium citrate solution, electrargol, liver extract, 20 per cent solution of sodium hyposulfite, horse serum, injectable amino-acids, high vitamin diets, ovarian preparations, and so forth, without any effect whatever. The only substance they found to be of any value was a 1 per cent solution of Congo red, 1 cc. for every 8 to 10 kg. of bodyweight. This substance seemed to be of great value in the treatment of hemophilic accidents, particularly in the joint cases.

Purpura. Types and Etiology. There are, broadly speaking, 2 types of purpura: (1) a type in which the blood platelets are normal but the capillaries are defective (nonthrombocytopenic purpura), and (2) a type in which the platelets are strikingly deficient, the capillary walls being normal (thrombocytopenic purpura). The former type is undoubtedly much more common, being associated with serum sickness, infections of various types, snake bites, senility, and so forth. In women, the reviewer has noticed its frequent association with the menstrual period. The hemorrhagic state in association with chronic nephritis with uremia is interesting and is discussed by A. Gualdi (*Policlinico* **42:** 136 [Mar.] 1935). The purpura of uremia is in all probability "toxic" in type, being associated with humoral changes of a physicochemical nature originating in complete insufficiency of the kidney and partial insufficiency of the liver. Gualdi states that the hemorrhagic manifestations of the skin or mucous membranes are not seen in chronic nephritis unless chronic uremia is present.

Purpura of the thrombocytopenic (platelet-

*Part of this mystery has been dispelled in some interesting recent work by A. J. Patek, Jr., and R. P. Stetson (J. Clin. Investigation **15**:531, Sept., 1936), who found that normal plasma contains a substance lacking from the plasma of hemophiliacs.

deficiency) type is present as an idiopathic disorder, or as a hypersensitive or toxic reaction to certain drugs or as a symptom of some such destructive process in the marrow as leukemia or metastatic malignancy or of aplasia of the marrow, as in benzol poisoning, and so forth. The importance of drugs as causative agents in certain cases of "idiopathic" purpura hemorrhagica is just being appreciated. A few years ago, "sedormid" was definitely implicated as the cause of 3 cases of purpura (see F. E. Loewy, *Lancet* **1:** 845 [April 21] 1934), and the author indicated that certain patients might be hypersensitive to the drug. The reviewer has had occasion recently to study some interesting cases of drug hypersensitivity with symptomatic thrombocytopenic purpura. It thus becomes apparent, first, that the more we study idiopathic disorders, the less idiopathic do they become, and, secondly, that hypersensitivity to drugs may result not only in general reactions, but in skin eruptions and such bone-marrow reactions as agranulocytosis and thrombocytopenic purpura. W. S. Middleton and O. O. Meyer (*Ann. Int. Med.* **8:** 1575 [June] 1935) bring out that the same drug may cause either complete marrow insufficiency (aplastic anemia), leukopenia, or thrombocytopenia. This is true particularly of gold and arsenical compounds. E. H. Hudson (*Lancet* **2:** 74 [July 13] 1935) reports 2 cases of thrombocytopenic purpura caused by administration of gold and arsenical compounds and conclude that an idiosyncrasy or abnormal sensitivity on the part of the patient is the probable cause.

Treatment. S. M. Peck and N. Rosenthal (*J. A. M. A.* **104:** 1066 [Mar. 30] 1935) describe the effect of moccasin snake venom in the treatment of hemorrhagic conditions. Snake venom in ordinary dosage causes hemorrhage by capillary rupture; if this material is given in gradually ascending doses, beginning with 0.4 cc. of a 1:3000 solution, the capillaries become refractory to the "Schwartzman phenomenon". The injections are given, as a rule, twice weekly subcutaneously, 0.8 cc. being the maximum dose. With marked bleeding, the period between injections is shortened. Treatment is continued for 2 to 3 months, and if the patient has shown a good response, the interval between injections is lengthened. In children, the minimum dose is 0.2 cc. (3 minims) of the 1:3000 solution, the maximum dose 0.6 cc. (10 minims). Ecchymotic reactions are common and most of the patients become hypersensitive to the material. This necessitates desensitization and injections are again given twice weekly beginning with 0.1 cc. (1½ minims) of a 1:10,000 solution. All types of hemorrhagic disorders were treated: idiopathic nasal bleeding, functional uterine bleeding, nonthrombocytopenic purpura, thrombocytopenic purpura, bleeding in association with hereditary hemorrhagic telangiectasis and hemophilia. There was great improvement in most of the cases, although no improvement took place in hemophilia or in leukemia. H. M. Greenwald (*Am. J. Dis. Child.* **49:** 347 [Feb.] 1935) states that of 8 cases of thrombocytopenic purpura treated with splenectomy and repeated transfusions from 1928 to 1932, two died of cerebral hemorrhage and one of postoperative shock. In 3 recent cases treated with moccasin snake venom, the bleeding stopped in each case after the third or fourth injection, and the bleeding time became reduced. The blood platelets also were increased. (Although these results seem at first glance to be remarkably good, they have yet to stand the test of time and of critical appraisal.)

POLYCYTHEMIA

The arbitrary distinction between polycythemia "vera" and secondary polycythemia may be more apparent than real and of no greater moment than that between "primary" and "secondary" anemia. All cases of anemia are secondary to some cause, and it may well be that the same holds true for polycythemia. Paul Reznikoff, N. C. Foot, and J. M. Bethea (*Am. J. M. Sc.* **189:** 753 [June] 1935) make some observations regarding the etiologic and pathologic factors in polycythemia vera. They found that of 134 patients with the disease, 48 per cent were Jews born in Eastern Europe. (The average incidence of this group in the 6 hospitals studied was under 10 per cent.) Since this racial incidence was roughly similar to that in thromboangiitis obliterans, study of the blood vessels of the bone-marrow was considered important. In all of the polycythemia vera cases studied there was distinct thickening of the capillary walls due to fibrosis of the subintimal and adventitial layers. In an early case of the disease marked inflammatory and necrotic lesions were seen along the course of the blood vessels in the marrow. There was "frequent" association of polycythemia vera with thromboangiitis obliterans. Reznikoff and his associates speculate whether the vascular defect in the marrow may not cause an anoxemic state, with resultant compensatory increased red cell production. (It should be mentioned that at the present state of knowledge, it is difficult to state definitely whether the vascular lesions of the bone-marrow are the primary condition or whether they are secondary to continued distention of blood vessels with an increased volume of blood.)

The vascular lesions in polycythemia vera are indeed striking and one of the most striking of these is the frequency of thrombotic manifestations. R. Jürgens and K. Bach (*Deutsches*

Arch. f. klin. Med. **176:** 626 [Aug.] 1934) observed 7 cases of polycythemia of which 3 presented thrombosis. The patients with thrombosis showed increase in blood platelets, shortening of the bleeding time and an increase in the blood fibrinogen and globulin. These findings were absent in the 4 cases free from thrombotic manifestations.

Treatment. Treatment is eminently unsatisfactory. Venesections, x-ray therapy to the bones, and phenylhydrazine or acetylphenylhydrazine hydrochloride are all being used and each has its adherents. M. Sgalitzer (*Wien. klin. Wchnschr.* **48:** 675 [May 18] 1935) tried x-ray irradiation of the entire body, using somewhat larger doses than are employed in leukemia. Daily dosage of about 25 roentgens is given for 1 week, after which the blood is examined with particular reference to the leukocyte count. It is dangerous to continue irradiation with a white count lower than 3000 per cu. mm. If the leukocyte count is maintained, the irradiation is continued. Reactions to the treatment vary considerably. Relapses occur in from 18 months to 5 years. A very interesting method is that proposed by F. Reimann and A. Breuer (*Ztschr. f. klin. Med.* **128:** 238, 1935), who produced what amounts to hypochromic (iron deficient) anemia in their 7 cases by removing 300 to 400 cc. of blood twice weekly. Diminution in the iron stores of the blood resulted in diminution in erythropoiesis and thus in a remission of the disease which lasted for several months to 2 years. They compare this method of treatment with x-ray irradiation and the administration of phenylhydrazine. X-ray irradiation, they feel, is dangerous on account of the extraordinarily high dosage which must be given; with phenylhydrazine the marrow becomes stimulated and the treatment must be continuously applied and the patient constantly followed because of the danger of poisoning.

AGRANULOCYTOSIS

Etiology. Paper after paper continues to present evidence indicating the importance of the role of drugs, particularly amidopyrine, in the etiology of agranulocytosis. H. Jackson, Jr. and F. Parker, Jr. (*New Eng. J. Med.* **212:** 137 [Jan. 24] 1935) doubt a good deal of the evidence which has been advanced regarding this relation. In a previous paper, H. Jackson, Jr. (*Am. J. M. Sc.* **188:** 482 [Oct.] 1934) states that in 74 per cent of his cases, drugs had either no causative relation to the disease or had not even been used by the patient prior to the attack. This view is not, however, concurred in by the great majority of observers. T. Fitz-Hugh, Jr. (*M. Clin. North America* **19:** 103 [July] 1935) discusses the question of etiology carefully and concludes that amidopyrine is a most important factor, producing the disorder by way of some, as yet unexplained, idiosyncrasy mechanism. He feels that since "amidopyrine is a drug of no outstanding value, its use should be discontinued until further evidence is at hand". Despite the feeling of most observers that the affected individuals must be in some way hypersensitive to the drug, most of the various tests for hypersensitivity have been negative, although T. L. Squier and F. W. Madison (*Wisconsin M. J.* **34:** 175 [Mar.] 1935) report positive "patch" tests to amidopyrine in 2 of their recovered patients. Recently the reviewer (W. Dameshek and A. Colmes: *J. Clin. Investigation* **15:** 85 [Jan.] 1936) has obtained strikingly positive tests to the intradermal administration of amidopyrine after it had been allowed to come in contact with blood serum for several days. Tests with amidopyrine alone and with blood serum alone were negative. This suggests—following the observations of Landsteiner—drug protein linkage with the formation of a new sensitizing antigen. In the above experiments, the disease was induced in 2 recovered patients by the above intradermal tests, in which only a few milligrams of the drug had been introduced. F. T. Hunter (*New Eng. J. Med.* **213:** 663 [Oct. 3] 1935) from a study of the literature comes to the conclusion that certain individuals are unusually sensitive to various drugs, the sensitivity becoming expressed in the clinical picture of agranulocytosis. The drugs which have been most frequently associated with the development of the disease have been amidopyrine, drugs containing amidopyrine, and dinitrophenol. The devastating effects of the latter drug, not only in the production of agranulocytosis but in other serious conditions, are just coming to light.

Pathology. H. Jackson, Jr. and F. Parker, Jr. (loc. cit.) discuss the very variable descriptions of the bone-marrow given by various authors. In Jackson's experience of 25 typical cases dying of the disease, the marrow was found to have either a normal or increased cellularity. There was no disturbance in either erythropoietic or megakaryocytic formation, but marked changes were present in the cells of the granular series. No mature granulocytes were found and practically every cell was decidedly immature. In those cases surviving the disease for from 8 to 20 days, many lymphocytes and plasma cells were found. Jackson and Parker are inclined to agree with the view of Fitz-Hugh and Krumbhaar that the marrow in these cases indicates a "maturation arrest" of myeloblastic cells.

R. P. Custer (*Am. J. M. Sc.* **189:** 507 [April] 1935) makes much the same observations. In 9 of 11 cases studied at autopsy, uniform appearances were present: proliferation of myeloblasts with "maturation arrest" so that only

few myelocytes and mature granulocytes were present, a normal or even slightly increased red cell formation, and infiltration of lymphocytes.

It is possible at the present time to build up a fairly consistent line of physiologic reasoning which explains the sequence of events in agranulocytosis: a certain few people are extremely sensitive ("allergic") to such drugs as amidopyrine; the bone-marrow becomes suddenly involved in a specific manner and there is a paralysis of maturation of cells of the granulocytic series; the granulocytes disappear from the blood; in a few days, secondary bacterial invaders appear and the clinical picture of agranulocytosis is present. Treatment with nucleic acid derivatives might have a direct effect in the development of normal maturation of the cells.

Treatment. Jackson and Parker (loc. cit.) state that, although many measures have been advocated to combat agranulocytosis, none are specific. Nonspecific therapy (injection of whole milk, and so forth), transfusion of blood, stimulating doses of x-ray, liver extract, and certain derivatives of nucleic acid have been advocated. These authors feel that the patient has the best chance with a mixture of pentose nucleotides (pentnucleotide). Of 103 patients treated with this drug, which is given intramuscularly twice or three times daily in doses of 10 cc., 69 or 67 per cent recovered and were alive at the time of writing. The mortality prior to the introduction of the drug had been about 75 to 90 per cent. The reviewer feels that a more simple derivative of nucleic acid (that is, adenine sulfate) which is given intravenously in dosage of 1.0 gm. (15 grains) is somewhat more active and more free of reactions.

GLANDULAR FEVER (INFECTIOUS MONONUCLEOSIS)

This is probably one of the most commonly overlooked diseases in general practice. It is usually called "grippe" since it presents itself with fever, headache, and sore throat. Glands not ordinarily being looked for are frequently missed. The diagnosis should be suspected in a youngish individual who has an irregular, rather slight fever which tends to remit at intervals, and who complains of headache, some sore throat, at times even of abdominal pain. H. L. Tidy (*Lancet* **2:** 180 [July 28] 1934); C. A. McKinlay (*J. A. M. A.* **105:** 761 [Sept. 7] 1935), and B. K. Wiseman (*Cyclopedia of Medicine*, Revision Service, **13:** 151, 1936) present the various clinical features. An interesting symptom is severe abdominal pain, presumably due to enlarged mesenteric glands, and often misdiagnosed as appendicitis. The superficial lymph nodes are always enlarged, especially those of the upper cervical, submaxillary and suboccipital areas. It is curious but none the less true that in almost every case the left-sided cervicals and supraclaviculars are much more prominent than those on the right. The diagnosis is made in most cases by physical examination alone which shows an individual with fever, general lymph node enlargement, yet who does not appear at all ill. There is no anemia and no bleeding as seen in acute leukemia. Diagnosis is made positive by examination of the blood smear which shows extreme lymphocytosis, the lymphocytes being of many types: large, extremely large, those with indented nuclei, with heavy blue cytoplasm and so forth. The bizarre blood picture is quite in contrast with that seen in acute leukemia in which a monotonous blood picture is quite the rule. Wiseman states (loc. cit.) supravital preparations are superior to the ordinary stained smears because certain characteristics of nucleus and cytoplasm are lost in the latter. H. Downey and J. Stasney (*J. A. M. A.* **105:** 764 [Sept. 7] 1935) and C. A. Stuart, A. M. Burgess, H. A. Lawson, and H. W. Wellman (*Arch. Int. Med.* **54:** 199, 1934) describe the lymphocytes accurately. In the reviewer's hands, diagnosis from the stained blood smear alone has proved entirely satisfactory, and the heterophile agglutination test has proved more of scientific interest than a diagnostic help. The test does not seem to be positive in every typical case; it is, of course, satisfying (as absolutely ruling out leukemia) to obtain a strongly positive test. In recent articles by Stuart, Burgess, Lawson, and Wellman (loc. cit.), C. A. Stuart, J. Tallman, and E. Brintzenhoff (*J. Immunol.* **28:** 85 [Feb.] 1935), G. H. Bailey and S. Raffel (*J. Clin. Investigation* **14:** 228 [March] 1935) and others in which is discussed the theoretical significance of the agglutination phenomenon, no hint has as yet been obtained regarding its cause. It is likely that from it will some day come information about the etiology of the disease. In this regard, Bailey and Raffel (*J. Clin. Investigation* loc. cit.) state that the agglutination reaction is probably the specific response to an antigen having a factor in common with a thermostable component of sheep and ox red cells, a certain strain of B. Welchii, and possibly horse kidney. E. M. Butt and A. G. Foord (*J. Lab. & Clin. Med.* **20:** 538 [Feb.] 1935) suggest a quick microscopic test by using one loopful of blood serum to be tested mixed with 4 loopfuls of a 2 per cent suspension of sheep's red cells in a hanging drop preparation. In blood from infectious mononucleosis almost immediate agglutination takes place. Some cases are associated with severe fusospirochetal infections (Vincent's angina), and for these, as suggested by Wiseman (loc. cit.) peroxide gargles and one or two intravenous injections of neoarsphenamine hasten healing. Most cases, however, require nothing but symptomatic treatment. A feeling of "lack of pep" may persist for a month

to several months after fever and lymphadenopathy have subsided. The blood picture gradually returns to normal within 2 or 3 months; it is well to know that a second infection occurring within a year may be associated with lymphocytosis.

LEUKEMIA

The case reports concerning leukemia bulk large in hematologic literature and every year one seems to see more and more cases. Yet the outlook remains just as tragic as ever. Most investigators feel that the disease represents a highly malignant generalized neoplastic condition of one of the three blood-forming organs: the bone-marrow, the lymphoid system, and the reticulo-endothelial system. It is very likely that the localized neoplasms of these organs (chloroma, lymphomata, reticuloma, and so forth) are very closely related to the leukemic, or generalized conditions. The malignant character of leukemia and its relation to localized neoplasms are well brought out in an experimental study in rats by J. Furth (*J. Exper. Med.* **61:** 423 [March] 1935). An emulsion of spleen from a mouse dying of myeloid leukemia when injected into other mice at times produced leukemia, at times tumors, and at times a combination of tumor and leukemia. The type of condition which developed was dependent upon the route of entry, the resistance of the host and the character of the cells injected. Both "acute" and "chronic" types of leukemia developed. Furth felt that to classify leukemia into acute and chronic varieties was arbitrary, since they both were the same disease with different growth tendencies. What starts off the irreversible leukemic process is not known. Some hint might be obtained from those cases of leukemia which occur in workers exposed to much x-radiation. In a very interesting (Belgian) letter in the *J. A. M. A.* (**104:** 1921 [May 25] 1935) the remarks of Dr. Maisin to the Belgian Society of Radiology anent the morphologic changes in the blood of radiologists are reported. According to the correspondent, Maisin states that 25 per cent of radiologists are affected with lymphoid leukemia (! !). Two Belgian radiologists are said to have died of leukemia. Maisin states further that close regard to protection from the x-rays is imperative, particularly in therapy. L. F. Craver (*J. A. M. A.* **105:** 1820 [Dec. 7] 1935) in discussing the etiology of cancer refers to work by several authors concerning the development of various types of blood cell tumors and leukemia in mice following injections of such chemicals as indole, tar, and so forth.

The diagnosis of leukemia can either be the easiest thing in the world or the hardest. With the blood filled with large numbers of cells, almost all immature, the diagnosis should be made in every instance, whether or not the exact type of cell—myeloblast, lymphoblast, or monocyte—is differentiated. In the presence of a normal or even a low white cell count and anemia (at least one-half the cases present these features) the diagnosis may be more difficult. N. Rosenthal and W. Harris (*J. A. M. A.* **104:** 702 [March 2] 1935) discuss the difficulties in diagnosis from a review of 455 cases seen over a period of years. The important characteristic feature, they feel, is the persistent relative or absolute increase in number of mature or immature white cells. R. R. Kracke and H. Garver (*J. A. M. A.* **104:** 697 [March 2] 1935) emphasize the importance of recognizing the immature cells in the disease as well as the macrocytosis of the red cells which at times causes confusion with pernicious anemia. In children, particularly, the diagnosis may often be very difficult as brought out by A. F. Abt (*Pennsylvania M. J.* **38:** 389 [March] 1935) since leukemia may be confused with such totally different conditions as diphtheria, scurvy, endocarditis, rheumatic fever, von Jaksch anemia, Cooley's anemia, and so forth. What strikes the reviewer in seeing these cases is the blind faith so often placed by physicians in the hematologic reports of technicians. (This illustrates again the power of the written word, particularly on a laboratory report. With few exceptions technicians seem to call all types of cells with deep blue cytoplasm "lymphocytes" or "large mononuclears" whether they are lymphoblasts, myeloblasts or histiocytes.)

Interest in monocytic leukemia continues intense as these cases are more readily recognized. Good articles are contributed by V. Levine (*Folia. haemat.* **52:** 305, 1934); L. E. H. Whitby and J. M. Christie (*Lancet* **1:** 80 [Jan. 12] 1935); and C. A. Doan and B. K. Wiseman (*Ann. Int. Med.* **8:** 383 [Oct.] 1934). All of these authors agree that this type of leukemia is probably much more frequent than has heretofore been suspected. R. Isaacs (*The Cyclopedia of Medicine, Revision Service,* **13:** 153, 1936) cites various other types of leukemia which have been discriminated: plasma cell, eosinophilic, and megakaryoblastic.

The neurologic changes which occur in leukemia are often quite interesting and have been analyzed by R. S. Schwab and S. Weiss (*Am. J. M. Sc.* **189:** 766 [June] 1935). I. Goldstein and D. Wexler (*Arch. Ophth.* **13:** 26 [Jan.] 1935) studied the fundus oculi carefully in eleven cases. In most cases, the changes are minimal, in an exceptional case quite striking. In the reviewer's experience, the most marked changes occur in acute lymphatic leukemia when the retina may often be seen to be thick, edematous, and shiny. The bone changes in leukemia have been the subject of several articles. H. P. Doub and F. W. Hartman (*J. A. M. A.* **105:** 942

[Sept. 21] 1935) contribute a comprehensive article. "Moth-eaten" areas in the bones on the x-ray plate together with pin-point areas of decalcification in the flat bones are suggestive of myeloid or lymphatic types. L. F. Craver and M. M. Copeland (*Arch. Surg.* **30:** 639 [April] 1935) found bone changes in about 7 per cent of 86 cases of lymphatic leukemia; in only 1 of 84 cases of myelogenous leukemia. Children are especially prone to bone changes as noted by C. E. Snelling and A. Brown (*Arch. Dis. Childhood* **9:** 315 [Oct.] 1934) who found changes in 8 of 12 cases.

Very little advance has been made in treatment of this dreaded disease. Isaacs (loc. cit.) analyzes the 3 main types of therapy used: x-ray, transfusion of blood, and arsenic. This investigator advocates the minimum number (4 or less) of doses that are necessary to produce the desired result. He states that small repeated doses shorten the remissions and hasten the period in which most of the cells appear in the blast stages. H. Langer (*Am. J. Roentgenol.* **34:** 214 [Aug.] 1935) advocates treatment over the spinal column in order that the paravertebral ganglia might be irradiated and thus depress a (highly speculative) overactive sympathetic nervous system. The latter system has been previously related to leukemia: Friedgood some years ago found reduction in basal metabolic rate and in white cell count following Lugol's solution—this was interpreted as a possible action on an overactive sympathetic nervous system. W. Dameshek, D. D. Berlin, and H. L. Blumgart (*New Eng. J. Med.* **210:** 723 [April 5] 1934) more recently performed thyroidectomy in a case of chronic lymphatic leukemia with extreme hypermetabolism with excellent results.* M. C. G. Israëls (*Brit. M. J.* **1:** 1021 [May 18] 1935) treated five cases of chronic lymphatic leukemia, first with Lugol's solution, then with x-rays. He concluded there was no relation between lymphatic leukemia and hypermetabolism and therefore thyroidectomy was not at present justified. N. Rosenthal and W. Harris (loc. cit.) state that radiotherapy is of most value in chronic myeloid and lymphoid leukemia although results were temporary and resistance apt to develop. In contradistinction to most writers, Rosenthal and Harris feel that radiotherapy is justified in acute leukemia.

NEOPLASMS OF THE WHITE CELLS

An excellent article on "Lymphatic, Myelocytic and Monocytic Neoplasms" by H. P. Doub and F. W. Hartman (loc. cit.) gives most of the recent concepts regarding these diseases with especial reference to roentgen diagnosis and treatment. Here are presented cases of lymphosarcoma terminating as lymphatic leukemia, chloroma (myelosarcoma) and Hodgkin's disease. Callender's classification referred to in last year's review is also utilized by Doub and Hartman. There are three types of white cells (granulocytes, lymphocytes, monocytes) derived from the three blood-forming organs (bone-marrow, lymphoid tissue, and reticulo-endothelial system) and which are subject to either general or local proliferation. General proliferation is leukemia; local proliferation results in a tumor. There are bone-marrow, lymphoid, and reticuloendothelial tumors. These may be highly malignant (sarcoma) or only slightly malignant. Gradations in types of malignancy are frequently seen. An incomplete list of these tumors is as follows:

Bone-Marrow	: Myelosarcoma (Chloroma)	; Myeloma
Lymphoid Tissue	: Lymphosarcoma	; Lymphoma
	:	; Plasmacytoma (Multiple Myeloma)
Reticulo-Endothelial Tissue	: Reticulum Cell Sarcoma	; Reticulo-endothelioma
	: Hodgkin's Disease	

It is noted from this list that "multiple myeloma" is a misnomer, and it is in reality a tumor of lymphoid cells (plasma cells) which, like most blood cell tumors, tend to invade bone. It is also noted that Hodgkin's disease is included among the reticulo-endothelial tumors, where many pathologists now place it. Regarding Hodgkin's disease, Edith L. Potter (*Arch. Path.* **19:** 139 [Feb.] 1935) states there is a proliferation of reticulum cells along both normal and abnormal lines. Some of the abnormal cells develop into typical "Hodgkin" cells which are very large with basket-shaped nuclei either single or multiple in type. According to Potter, Hodgkin cells are never found except in Hodgkin's disease. A good deal of attention is being paid to "multiple myeloma" (plasmacytoma) and more particularly to the changes in the blood protein which occur in association with it. A. G. Foord (*Ann. Int. Med.* **8:** 1071 [March] 1935) found marked hyperproteinemia in 3 of 4 cases together with autohemagglutination of the red cells. It is remarked that the findings of either a very high blood protein or of marked rouleaux formation of the red cells either in smears or in hemocytometers should make one suspect the presence of the disease. Helene Bürkel (*Ztschr. f. klin. Med.* **127:** 552, 1934) demonstrates that, in various diffuse and localized disturbances of the bone-marrow, the blood protein values do not deviate greatly from the normal. Hyperproteinemia is seen only in "myeloma", although it does not occur in every instance of the disorder.

*This patient is still alive and well after 3 years. One year after striking improvement had occurred, all of the symptoms and signs were reinduced by large doses of thyroid.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 22471

PRESENTATION OF CASE

A 52 year old French Negress was admitted complaining of cough and dyspnea. The patient's son, who is 18 years old, stated that her age was nearer 35 than the given age of 52 years.

About one and a half years before entry the patient began to feel run down and was readily fatigued. At this time she had an attack of pneumonia which confined her to bed for 4 weeks. There was cough and fever of 102° to 103° with chilly sensations and rusty sputum. The cough gradually subsided and the temperature became normal. Six months later she had another attack of pneumonia and subsequently developed a dry hacking cough accompanied by a sore throat, which persisted for 2 or 3 weeks. There was no associated fever. The cough occurred only a few times a day and was usually excited by exertion or talking. During the 3 months preceding entry the cough became progressively worse and occurred in paroxysms, often lasting as long as 6 to 10 hours. The cough was generally unproductive but occasionally in the morning she raised as much as one half to a cupful of creamy material which was occasionally blood streaked. This she stated came from the throat rather than the lungs. During particularly severe paroxysms the right side of her neck swelled and became firm. This was both palpable and visible to the patient and disappeared directly after cessation of the cough. Dyspnea appeared as the severity of the cough increased and the patient complained of inability to get enough air into her chest. For six months before admission she required two pillows in order to rest comfortably at night. More recently it was necessary for her to sit bolt upright with her head in her hands throughout the night. Throughout the illness the patient noted swelling of her feet and legs up to the knees which increased in severity during the last 3 or 4 months. This swelling was worse at night and was relieved by bed rest. The patient complained that she had insufficient funds for adequate food and often went for 1 or 2 days without eating. Her appetite, however, was unimpaired.

Three years before entry because of poor finances the patient had insufficient food and her weight decreased from 150 to 120 lbs. in 3 months. She went to a sanatorium where she remained for 4 months, 1 month of which was spent in bed. For 5 or 6 years she had fleeting sharp pains over the precordium about two or three times a year. This usually occurred following moderate exertion. Occasionally pain radiated along the inner aspect of the left arm to the elbow. Eighteen years ago she had double pneumonia with pleurisy.

Physical examination showed a well-developed and nourished orthopneic Negress. The mucous membranes were somewhat pallid. Oral hygiene was poor and the throat was negative. Several small nodes were palpable at the angles of the jaw. The heart was slightly enlarged to the right, the right border of dulness being 3 centimeters from the midsternal line. The sounds were regular and P_2 was greater than A_2. A soft blowing systolic murmur was audible in the aortic area and a similar murmur was audible at the apex. No diastolic murmurs were heard. A few scattered rales were audible at both bases but the lungs were otherwise clear. The blood pressure was 110/80. The liver extended two fingerbreadths beneath the costal margin and was slightly tender. The abdomen was otherwise negative. There was pitting edema of the feet and legs, more marked on the right. The patient was menstruating and a pelvic examination was not done.

The temperature was 99°, the pulse 90. The respirations were 20.

Examination of the urine showed a specific gravity of 1.005 with a slight trace of albumin. The sediment was negative. The blood showed a red cell count of 4,000,000, with a hemoglobin of 75 per cent. The white cell count was 5,500, 61 per cent polymorphonuclears. The sputum showed no tubercle bacilli. Stool examinations were negative. A Hinton test was negative. The nonprotein nitrogen of the blood was 33 milligrams. The serum protein was 4.6 grams, and the cholesterol 148 milligrams. The sedimentation rate was 0.1 millimeters per minute. An electrocardiogram showed a tendency toward right axis deviation. T_1 was low and T_2 and T_3 inverted. S-T_4 was flat and T_4 was small and diphasic. A phenolsulphonephthalein test showed 60 per cent excretion of dye.

X-ray examination showed that the heart was slightly increased in the transverse diameter. Both hilar shadows were increased in size, apparently due to enlargement of the pulmonary vessels. The lung fields and costophrenic angles were clear.

The patient was treated palliatively by bed rest, salyrgan, and small doses of digitalis. She improved gradually and during the third hospital week two basal metabolic rates were —17 and —8. Throughout the hospital stay, except for occasional rises to 100°, her temperature remained normal. The edema disappeared but recurred to a slight degree when the patient arose from bed. She was discharged improved on the fifty-eighth hospital day.

Second Admission, one week after discharge.

The patient had refused sanatorium care and returned to the home of a friend. Here she felt well, was able to get up and about but still continued to have some dyspnea and slight puffiness of the dorsa of both feet. Three days before reentry, shortly after drinking a glass of water, she had dull, steady, nonradiating epigastric pain which continued until admission. There was some nausea and the water ingested was vomited. She vomited repeatedly following any attempt to eat or drink. Dyspnea recurred and progressed rapidly to orthopnea and the edema of the lower extremities became pronounced. On the day before entry she took a train to Boston and upon arrival appeared so ill that she was immediately admitted to the Emergency Ward.

Physical examination showed the patient to be markedly orthopneic and the lips were slightly cyanotic. The heart showed no change in size but a loud blowing precordial systolic murmur was heard best at the left third and fourth interspace. The sounds were regular and of good quality. The blood pressure was 100/60. A few basal rales were heard in the lungs and the liver extended down about two or three fingerbreadths. There was pitting edema of the legs up to the knees.

Examination of the urine showed a slight trace of albumin and the sediment was loaded with white blood cells. The blood showed a white cell count of 9,000.

On the morning following entry she called for help. When the nurse arrived the patient was pulseless and unconscious. She was pronounced dead 5 minutes later.

Differential Diagnosis

Dr. Howard B. Sprague: I think one should approach this case by asking first the question —did this patient have primary cardiac disease? There seems to me to be very little evidence that that was true. There were no valvular murmurs. She had only a slight systolic murmur at the base of the heart and over the pulmonary area, with very little enlargement of the heart. She was in the hypertensive age period and apparently also at the arteriosclerotic age, but we have no signs of either, and there was no evidence of lues. The more obscure types of primary cardiac disease do not appear from any evidence that we have. The basal metabolic rates were within limits which would not make one think of thyroid disease. I suppose in a discussion of the case that the question of her low food intake might have been brought up in relation to edema, because her plasma protein was down around the critical level for edema, or because of the present interest in lack of proper vitamin intake, particularly vitamin B. Cardiac disease of unexplained origin is at the moment thought in some cases to be due to this vitamin deficiency.

If we cannot diagnose primary cardiac disease, we are nevertheless confronted with dyspnea, orthopnea, edema and cough to be explained on some basis. There is evidence of secondary cardiac strain with the note that the right side of the heart was somewhat enlarged, that there was a tendency to a right axis deviation by electrocardiogram. There was some enlargement of the pulmonary vessels by x-ray. Electrocardiogram does not help very much as I imagine by the time that it was taken the patient had had some digitalis and that the inversion of the T waves may have been related to that. Therefore, if this is an instance of secondary cardiac effect it seems as if the strain were on the right heart (cor pulmonale) and therefore there was some difficulty in the lesser circulation. That would mean either something in the vascular tree, or in the air containing elements of the lung, or in the mediastinum, to interfere with the functions of these systems which would secondarily produce strain on the right heart.

So far as the vessels in the lungs are concerned one might question the possibility of endarteritis obliterans, so-called Ayerza's syndrome, thought by some to be due to lues, but the fact that cyanosis was not an outstanding feature here would seem to be against that. The Hinton test was negative. There does not seem to be anything described to us in the periphery of the lungs so far as the air containing elements are concerned, such as pulmonary fibrosis or fibroid phthisis, or anything of that sort which would produce strain on the right heart.

We are led to look in the middle of the chest, in the mediastinal region, for whatever pathology is present. There is no clear evidence of any mediastinal tumor and no signs of aneurysm which would interfere with the circulation or with breathing. But it does seem to be rather an obstructive lesion. We have in favor of that the paroxysmal and very prolonged attacks of cough, and the feeling of the patient that the sputum which she raised came from high up in the throat rather than from the lungs. There is evidence of what seems to be a herniation of the lung at the right apex, a

position where true hernia could occur. I have no better explanation for that description of the swelling in the neck. Then there is the sensation of inability to get enough air into the chest and orthopnea out of proportion to the degree of cardiac failure, as indicated by rales at the bases of the lungs, or evidence of fluid in the pleural cavity, as though the orthopnea might possibly be a choice of a position in which obstruction was less distressing. To explain that we have what seem to be most likely, malignancy of the lung, carcinoma of the bronchus, lung abscess or bronchiectasis, with a secondary cardiac effect.

As for malignancy, we cannot bring in the age of the patient as it is unknown. I do not know whether it is for or against malignancy. I do not think the nodes at the angles of the jaw mean very much. There is relative absence certainly of fever and leucocytosis, and a normal sedimentation rate. Against malignancy there is the absence of pain or frank hemoptysis, apparently lack of cachexia, the absence of the wheezy or stridulous type of breathing, and the fact that the patient improved and was able to leave the hospital.

So far as infection is concerned, either lung abscess or bronchiectasis, the story starts with what seems to be a frank infection, with fever, rusty sputum and a story of pneumonia. That may be a red herring across the trail. She apparently got over it and started with some other sort of pulmonary infection, without fever; but all her life she was susceptible to pulmonary infection. There is a large amount of sputum. It is difficult to see where a cupful of sputum could come from at one time, unless we are dealing with some sort of pathology up in this region. If there was a lung abscess there was rupture into a bronchus.

About her final entry in the hospital, this rather sounds as if something had happened in relation to her drinking the water and suggests a rupture of some sort into the mediastinum from the process, whatever it is, involving the pulmonary tree, perhaps this being responsible for her downhill progress. The final event is rather difficult to explain, that is whether it was cardiac asphyxiation or a hemorrhagic type of death. There does not seem to be enough in the cardiac examination to make us think it was cardiac in origin, unless one assumes some unusual thing like rupture into the pericardium or cardiac tamponade. It does not seem like asphyxiation. If something rose and choked her to death she could not get enough air out to cry for help. She died in five minutes. She may have had erosion of some vessel and some hemorrhage into the mediastinum. In summary, I think that the cardiac effects were secondary to pathology of the lung. What was thought to be enlargement of the pulmonary vessels by x-ray might possibly have been mediastinal pathology, and perhaps this process, whether abscess or bronchiectasis, involved more the right and upper part of the midchest.

X-ray Interpretation

Dr. George W. Holmes: These films show surprisingly little, as stated in the interpretation from the record. The heart shadow is definitely abnormal. It is distinctly enlarged to the right in the auricle. I do not see anything in the lung whatever except this shadow here which I take to be the nipple. We have two oblique films, a right and a left. There is considerable prominence in the region of the left auricle and pulmonary conus, with more or less bulging into the mediastinum. I think both auricles are dilated.

Clinical Discussion

Dr. Tracy B. Mallory: This is obviously a very difficult case. I wonder if there are any suggestions to be made.

A Physician: Was there any examination of the sputum or any statement about its character.

Dr. Mallory: I do not think she brought up any large amount in the hospital.

Dr. Aubrey O. Hampton: I think that question comes up very often. Patients say they bring up sputum and the chest is negative. I think it should be laughed off more than it is.

Dr. Mallory: I would like to read two consultants' notes, both of them surprisingly correct. Dr. Paul D. White: "There is no doubt about the structural diagnosis of some cardiac enlargement, evidently mainly right ventricular with prominence of the pulmonary artery and its branches, and congestive failure slowly clearing under treatment, but the etiologic diagnosis is obscure. The most likely factor in relation to the history of repeated respiratory infections, the electrocardiogram, and the absence of other evidence of trouble, is the cor pulmonale from pulmonary disease or pulmonary endarteritis obliterans. I can find no definite indication of rheumatic heart disease or congenital heart disease, or of primary left ventricular strain and failure, any one of which might account for right ventricular strain or failure. One must think, however, of the possibility of a previous hypertension which has finally caused strain and failure of the right ventricle with the subsidence of pressure to a low level. . . . There is an aortic systolic murmur which, however, does not seem to be prominent enough to allow a diagnosis of aortic stenosis. In this race lues is always to be thought of also, but there is nothing that confirms such a diagnosis here. I would recommend a pulmonary consultation to see if the pulmonary consultant thinks there may be enough pathology in the

lungs or pulmonary circulation to account for enlargement and failure of the right ventricle. All the trouble has come since her pneumonia of a year and a half ago. She had no symptoms whatsoever before." Dr. Donald S. King: "Cough the presenting symptom, but no purulent sputum. Physical examination shows rales, like congestion, at the left base in back. There is no clubbing of the fingers. X-rays negative so far as lungs are concerned. The only pulmonary process which would explain the picture is bronchiectasis behind the heart, but there is no real evidence of this in oblique films. There is no emphysema. I do not believe a pulmonary process will explain the cardiac changes."

Clinical Diagnoses

Coronary heart disease.
Congestive heart failure.
Chronic vascular nephritis.

Dr. Howard B. Sprague's Diagnosis

Cor pulmonale, probably secondary to pathology in the lungs, such as bronchiectasis or lung abscess producing chronic cough.

Anatomic Diagnoses

Pulmonary thrombosis, bilateral, ? primary.
Pulmonary embolus, terminal.
Pulmonary infarct, fresh.
Pulmonary endarteritis?
Cor pulmonale.
Thrombus of the right auricular appendage.
Leiomyomata uteri.
Endometriosis of the ovaries.
Adenoma of the adrenal cortex.

Pathologic Discussion

Dr. Mallory: We found at postmortem a very definite cor pulmonale. The interest in this case lies in its cause. I think we can show you in this colored plate. There lie the lungs with the pulmonary artery opened in situ and you can see that the main pulmonary artery and the chief branches to the right and left lung are almost completely filled with a pinkish gray thrombus. This gray thrombus was quite firmly adherent in gross, and seemed completely organized; but microscopically we found that only the peripheral parts were organized, the central and the superficial parts were not. A pretty careful search throughout the lung failed to show any bronchiectasis or anything from which she could have raised a cupful of sputum. The bronchial tree was entirely negative. Besides the older thrombus in the pulmonary artery we found several partially adherent red and evidently fresh ones in the branches of the upper lobe of the left lung, the apex of which showed evidence of early infarction. We found also a thrombus in the right auricle of the heart.

The rest of the autopsy was essentially negative except for fibroids of the uterus and endometriosis of the ovaries. We made a very careful search of the leg veins and pelvic veins for a possible source of pulmonary emboli without being able to find anything. It at first seemed possible that this thrombus in the right auricle might have been the source of pulmonary emboli but the microscopic examination helps us out to a certain extent by showing that the auricular thrombus is a very fresh and recent one, whereas most of the lesions in the lung are obviously much older. It probably was, however, the source of the fresh emboli and the pulmonary infarct in the upper lobe. As for the primary difficulty, we have to assume either multiple emboli far in the past for which we have no history and no source, or that we are dealing with one of these cases of primary thrombosis of the pulmonary arteries. The minute arteries through both lungs showed marked intimal thickening and evidence of thrombosis and recanalization obviously of many months' duration. Although I think it would be impossible to be sure in this case, primary endarteritis seems a reasonable bet. There is as much evidence for it as there is in most cases in which that diagnosis has been made. It is very similar to a case which Frothingham reported 2 or 3 years ago.

Dr. Sprague: Was there any herniation of the lung?

Dr. Mallory: It was not noticed.

Dr. Sprague: I have never seen a case of this sort, with the primary trouble in the pulmonary vessels, in which cyanosis was not a prominent feature. Perhaps the race of this patient was confusing. However, we must realize that this is the disease (Ayerza's disease) that is described as being common in South America, and that there the patients are dark skinned individuals. Cyanosis is an outstanding sign in these cases. In fact the cyanosis is so marked that they are known as "cardiacos negros" or "black cardiacs". Perhaps we are not keen enough to recognize cyanosis in a Negro.

A Physician: Do you think the pulmonary infarcts had been there for some time?

Dr. Mallory: No, they were very fresh. That is the episode that brought her into the hospital the last time and then a final pulmonary embolus was the immediate cause of death. The old thrombus had evidently been there for months, probably about a year.

CASE 22472

Presentation of Case

A 32 year old Italian waiter was admitted complaining of dyspnea.

About 16 months before entry the patient first noted that climbing a hill, which had pre-

viously afforded him no discomfort, now caused considerable dyspnea. He visited a physician who told him that he had a "leaking valve" and treated him with what was presumed to be digitalis. After 2 weeks of this treatment the patient felt better and returned to his work. Six weeks before coming to the hospital he developed a severe cough and was told by a physician that he had bronchiectasis. Shortness of breath now recurred and he was compelled to get out of bed at night and go to an open window for relief. He became unable to sleep unless he was propped up with several pillows. Occasionally his breathing was wheezing in character and his activity was markedly curtailed. About 5 weeks prior to admission he had a vomiting spell which was so severe that he could not catch his breath. At the same time he noted some cyanosis of his lips and face. There was frequent palpitation after any exertion and occasionally his heart seemed "to stop and twist about in his chest". Two weeks ago he first noted edema of the ankles which persisted and he was compelled to discontinue work. He began to have a constant pressing pain in the right upper quadrant. At no time was he confined to bed. Shortly before coming to the hospital he again began to vomit.

Ten years before entry he had chilly sensations and fever for some time. Shortly afterward he was treated for a septic hand and blood poisoning. Five years ago for a short time he had frequent shooting pains in the chest and an examination at that time showed a normal heart.

Physical examination showed a well-developed and nourished man with flushed facies, sweating profusely. He was markedly cyanotic, orthopneic, and the right neck veins were engorged. The pupils were dilated but reacted to light. The apex impulse was felt in the fifth interspace 12 centimeters from the midsternal line. It was pounding in character and imparted a systolic thrill. Coarse systolic and late diastolic rumbling murmurs were audible at the apex and loud rumbling systolic and early diastolic murmurs were heard at the aortic area. The blood pressure was 160/80 and a Corrigan pulse was observed. The right chest was dull below the level of the fourth rib and flat beneath the angle of the scapula. Rales were heard at the lower half of the left chest. The liver extended 4 to 5 fingerbreadths beneath the costal margin. The abdomen was distended and some dulness was elicited in the flanks. Both legs were definitely edematous.

The temperature was 99.5°, the pulse 90. The respirations were 30.

Examinations of the urine showed a specific gravity from 1.008 to 1.034. Large traces of albumin were consistently present and the sediments showed occasional white blood cells and 0 to 15 red blood cells with occasional hyaline and granular casts. The blood showed a red cell count of 5,780,000, with a hemoglobin of 75 per cent. The white cell count was 11,400, 78 per cent polymorphonuclears. A stool examination was negative. A Hinton test was negative. A blood culture showed no growth. The sedimentation rate was 1.21 millimeters per minute. An electrocardiogram showed partial A-V block with a P-R interval of 0.25 seconds. P_1 and P_2 were prominent and notched and there was moderate right axis deviation.

X-ray examination showed dulness obliterating the lower half of the left lung field, obscuring the diaphragm and left border of the heart. The dulness had a curved upper border. The lower half of the right lung field was mottled and the diaphragm obscured. The heart was shifted to the right.

The patient's temperature fluctuated irregularly between 98° and 102°. A tap of the right chest on the day of entry yielded 1,000 cubic centimeters of amber-colored fluid with a specific gravity of 1.008. A cell count showed 850 red blood cells, 52 lymphocytes, and 1 monocyte. The protein content was 1 per cent. Culture showed no growth. The nonprotein nitrogen of the blood was 28 milligrams. His white blood cell count gradually rose to 26,000. He became nauseated and vomited several times. Digitalis was discontinued and on the sixth day a left chest tap yielded 445 cubic centimeters of slightly blood tinged fluid with 19,150 red blood cells, 1,900 polymorphonuclears, 980 lymphocytes, and 10 monocytes. The specific gravity was 1.010 and the protein content 3.2 milligrams per cent. Cultures were negative. His condition became precarious and he suffered hemoptysis on several occasions. At the end of the third week an electrocardiogram showed auricular fibrillation with a ventricular rate of 50. T_1 was low and T_2 and T_3 inverted. On the twenty-fifth day he suddenly developed marked dyspnea which was partially relieved by an oxygen tent. Four days later a pleuropericardial friction rub became audible. No details relative to it were noted. He rapidly developed anasarca, became psychotic, and died suddenly on the thirty-fifth hospital day.

Differential Diagnosis

Dr. William Paul Thompson: From the description of the examination of the heart it seems evident that this patient was suffering from valvular disease, and that mitral stenosis and mitral and aortic regurgitation were present. Aortic stenosis to some degree is also probable because of the loud aortic systolic murmur, even though the confirmatory aortic systolic thrill is not described. If mitral stenosis was present, there is but one etiologic factor to be considered, and that is rheumatic fever. While

there is no definite history of past rheumatic infection, the "chilly sensations and fever for some time" ten years before entry may well represent active rheumatic infection.

The history during the sixteen months preceding death is one of increasing failure of the left ventricle, as evidenced by the dyspnea, and due to the aortic valve disease, or one of increasing pulmonary congestion due to the obstruction to outflow of blood from the lungs occasioned by the mitral stenosis. The severe cough which was present during the six weeks preceding entry is further evidence favoring either one of these factors in an equal manner, but the occurrence of protracted nocturnal dyspnea with wheezing (cardiac asthma) favors left ventricular failure due to the aortic valve disease as the more important factor. The edema and the pain in the right upper quadrant, the latter doubtless due to hepatic congestion, together with the engorgement of the neck veins noted on admission, are findings establishing the diagnosis of failure of the right ventricle, either secondary to failure of the left ventricle or to the strain imposed upon the right ventricle by the mitral stenosis of high degree.

The slight elevation of body temperature, the slight leukocytosis, and the prolonged P-R interval in the electrocardiogram on admission are factors pointing toward active rheumatic infection. The fever and leukocytosis, however, may both be due to the congestive failure, and it is not stated whether the digitalis, which had been prescribed at the beginning of symptoms sixteen months ago, and which might be the cause of the partial block, had been continued up to the time of admission. We cannot be certain, then, whether rheumatic infection was present, but I am inclined to believe it was, chiefly because if digitalis had been given in a quantity sufficient to produce P-R interval of this length, congestive heart failure of this severity would be unlikely. In favor of digitalis as the cause of this delay in auriculoventricular conduction is the history of vomiting shortly before the patient entered the hospital, which, however, may well be a part of the engorgement of the liver.

The occurrence of hemoptysis on several occasions, the increasing white blood cell count, the development of the friction rub, and the progressive downhill course all favor pulmonary infarction, due most likely to emboli but possibly the result of multiple thrombi as we have seen recently in a number of cases. The source of emboli is problematic. Of the two possible sources, the right side of the heart and the peripheral veins, I favor the latter as a more common seat of thrombi in congestive heart failure. The presence of auricular fibrillation which began sometime while the patient was in the hospital, suggests the right auricle as the seat of a mural thrombus. The sudden development of marked dyspnea ten days before death points also toward pulmonary embolism. The sudden death likewise points toward a large embolus obstructing the pulmonary artery at its bifurcation.

The electrocardiograms are of interest in that the prominence and notching of the P waves in leads I and II, together with the right axis deviation, make mitral stenosis almost certain. The low T wave in lead I and the inverted T waves in leads II and III described in the second electrocardiogram are almost certainly due to digitalis.

The case is somewhat unusual in that death in rheumatic heart disease followed the first failure, from which we may ordinarily expect a fair return of function in a young individual. We have learned, however, that active rheumatic infection and pulmonary infarction in the presence of failure are two things which make the prognosis exceedingly grave.

Clinical Diagnoses

Rheumatic heart disease.
Mitral and aortic stenosis and regurgitation.
Active rheumatic fever.
Congestive failure.

Dr. William Paul Thompson's Diagnoses

Rheumatic heart disease, probably active.
Mitral stenosis and regurgitation.
Aortic regurgitation.
Probably aortic stenosis.
Partial A-V block followed by auricular fibrillation.
Congestive heart failure of the right and left ventricles.
Pulmonary infarction, multiple.
Terminal massive pulmonary embolism.
Mural thrombus in the right auricle?
Thrombosis of peripheral veins, most likely in the pelvis or legs?

Anatomic Diagnoses

Rheumatic heart disease.
Endocarditis, chronic rheumatic, aortic; with stenosis, mitral and tricuspid.
Mural thrombus, right auricle.
Pericarditis, acute fibrinous.
Chronic passive congestion, liver, lung, spleen and kidneys.
Pleuritis, acute fibrinous, bilateral; left, marked.
Pulmonary infarct, right middle lobe.
Hydrothorax, bilateral; right, marked.
Pulmonary atelectasis, bilateral.
Pleuritis, chronic fibrous, bilateral.
Petechial hemorrhages, visceral pericardium and peritoneum.

Ascites, slight.
Renal infarcts, multiple, left, healed.
Edema, generalized.
Osteo-arthropathy of fingers.

Pathologic Discussion

Dr. Tracy B. Mallory: Cardiologists are rivaled only by the genitourinary surgeons in the accuracy of their antemortem diagnoses. Consequently we expect and generally learn that the important findings of the autopsy have been accurately predicted and the pathologist can hope to catch them only on the details and upon the complicating factors. This patient did have rheumatic heart disease with both aortic and mitral involvement. From the anatomic findings both stenosis and regurgitation must have been present at each valve ring though in each case the stenosis was by far the less important factor. We found in addition a definite tricuspid involvement. Evidence of acute rheumatism was lacking on the valves and in the myocardium, but was present in the form of an acute pericarditis and was probably also indicated by the presence of multiple petechial hemorrhages over the serous surfaces of the pericardium and the peritoneum. The heart was markedly and generally hypertrophied with dilatation of all the cavities. A thrombus was present in the right auricle and one pulmonary infarct was found to substantiate Dr. Thompson's prediction. Numerous infarcts were also found in the left kidney. Since the valvular lesions were apparently inactive, I think one must assume that there had also been at one time a thrombus in the left auricle. Large amounts of fluid had reaccumulated in the right chest, and the right lung was almost completely atelectatic. The liver, as might be expected in a case with tricuspid involvement, showed an unusually severe grade of passive congestion with considerable necrosis of cells in the centers of the lobules.

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THE NOBEL PRIZE IN MEDICINE 1936

IN conferring the Nobel Prize in Medicine upon Henry Hallett Dale and Otto Loewi, the Stockholm Committee has for the first time recognized pure pharmacology in its awards*; and by its action it has also given prominence to one of the newest and most highly significant fields of medical and biologic research, "the neuro-humoral transmitters". In 1914 Dale, after pointing out that acetyl-choline mimicked the actions of the cranio-sacral division of the autonomic system, much as adrenalin mimicked sympathetic innervation, wrote the following prescient sentence: "The possibility may, indeed, be admitted, of acetyl-choline, or some similarly active and unstable ester, arising in the body and being so rapidly hydrolysed by the tissues that its detection is impossible by the known methods. Such a suggestion," he added, "would acquire interest if methods for its experimental verification could be devised."[1]

*The previous awards in Medicine and Physiology are listed on page 992 with biographical notices of Professors Dale and Loewi.

Shortly before Dale's paper was published war had been declared, and, as Cannon points out,[2] men's thoughts were transferred to more urgent matters.

It remained for Otto Loewi, the well-known professor of pharmacology at Graz in Austria, to devise the means of verifying Dale's brilliant surmise. The story of how Loewi happened to perform the classical experiments that proved that acetyl-choline is liberated at the vagus nerve endings deserves to be recorded in detail. "One night, having fallen asleep while reading a light novel, he awoke suddenly and completely, with the idea fully formed that if the vagus nerves inhibit the heart by liberating a muscarin-like substance, the substance might diffuse out into a salt solution left in contact with a heart while it was subjected to vagal inhibition, and that then the presence of this substance might be demonstrated by inhibiting another heart through the influence of the altered solution. He scribbled the plan of the experiment on a scrap of paper and went to sleep again. Next morning, however, he could not decipher what he had written! Yet he felt that it was important. All day he went about in a distracted manner, looking occasionally at the paper, but wholly mystified as to its meaning. That night he again awoke, with vivid revival of the incidents of the previous illumination, and after this experience he remembered in his waking state both occasions. He set up a frog heart filled with Ringer's fluid, and after inhibiting the heart by stimulating the vagus nerve, found that the fluid had acquired a new property, that of being able to induce in another frog heart typical inhibitory vagal effects."[2]

Loewi's brief four page announcement[3] was greeted with considerable skepticism; a controversy followed, but in the end he was entirely vindicated and it is now believed that a substance akin to acetyl-choline is liberated wherever parasympathetic nerves end.[4, 5] The generalization, indeed, thanks to the work of Dale and his pupils, has been carried much farther. Only two years ago it was announced that acetyl-choline stimulated sympathetic ganglia,[6] and it was inferred that wherever *preganglionic* fibers of the autonomic system end, whether in Remak's ganglion of the heart or in the stellate ganglion of the thoracic sympathetic, there acetyl-choline is liberated when the preganglionic fibres are activated. Within the last year Dale and his pupils have caused us further to extend our ideas of the activities of acetyl-choline in the bodily economy, for the somatic motor nerves to skeletal muscles appear also to have their impulses transmitted to the contractile elements of the fibres through the agency of acetyl-choline.[7] If this is true, every motor fiber emerging from the central nervous

system, such as the sympathetic preganglionic fibers, the parasympathetic fibers and the somatic motor fibers, transfers its influence by means of acetyl-choline. If these generalizations are vindicated by future work, and it seems entirely probable that they will be, we can warmly congratulate the Stockholm Committee upon their courage in recognizing, while it is still in the process of being formulated, one of the greatest generalizations in the history of medical thought.

Those in this country who have played so conspicuous a part in unraveling the complementary story of neuro-humoral transmission of the peripheral sympathetic (as opposed to parasympathetic) impulses will undoubtedly rejoice to see the doctrines that they have helped to develop so fittingly recognized, and for their share they are deserving of equal praise.

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3. Loewi, O.: Über humorale Übertragbarkeit der Herznervenwirkung. I. Pflüger's Arch. f. d. ges. Physiol. **189**: 239-242, 1921.
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THE HOUSING PROBLEM

It is generally taken for granted that the standard of living in these United States is on at least as high a plane as any other country in the world. Consequently, the statement regarding housing conditions of low income families in this country, made by Dr. C.-E. A. Winslow of the Yale University School of Medicine before the American Public Health Association at their recent meeting in New Orleans, comes as a distinct surprise to many of us. He said that the homes of the poor in the United States, both in the tenement districts of the cities and in the impoverished rural communities, are much more unhygienic than those of similar groups in *any* of the leading countries of Western Europe.

It is well known that poor housing and high mortality rates go hand-in-hand. According to Dr. Winslow, however, public health authorities should not be content with merely lowering death rates. "Neither physical nor mental health nor fulness of living is possible when a whole family is crowded into a single room of a city tenement or struggling for survival in an unsanitary shack on an Appalachian mountainside." Not only must such homes be destroyed, but healthful ones must be provided at a cost to the dwellers that is consistent with their low incomes.

Dr. Winslow believes that this problem is one of the most urgent that faces health officials at the present time and that the need for proper housing facilities is so widespread that it can be properly handled only by "a permanent federal agency for housing and by a unified national policy, such as is proposed in the Housing Bill introduced by Senator Wagner at the last session of the Congress".

THE PRESENT CONFUSED SITUATION

Several months ago the American Foundation issued a letter to prominent and experienced physicians of the United States asking for opinions as to whether any essential changes are needed in the present organization of medical service. The recipients of these letters were requested to specify the direction of the opinions submitted, applicable to the following questions:

"Any form of insurance, voluntary or compulsory? The greater participation by the state in the provision of medical service to the people? Government subsidies without government administration? The extension of the public health services—and which of them—federal, state, local or all of these? Extension of community hospitalization, group clinics, public health nursing? More direct relation between medical science as represented by the leading physicians of the country and public health administration? Is it desirable or imperative that the medical profession through the medical societies should control standards, public health appointments, etc., how do you think that this end could best be achieved?"

The Foundation explained that it had nothing to advocate, had no preconceived objective, but proposed to summarize and present "the views of experienced men in the medical profession because they are the persons whose judgment should control".

The "member in charge" has stated that a considerable number of the most distinguished physicians in New England, particularly in Boston and New Haven, have already answered the inquiry. Several state medical journals have endorsed this movement and reports have been received to the effect that the chairman of the Bureau of Medical Economics of the American Medical Association has spoken favorably of the work of the Foundation.

The names of those associated with the American Foundation are as follows: Curtis Bok,

Esther Everett Lape, Karl T. Compton, Hugh L. Cooper, Thomas W. Lamont, Robert A. Millikan, James D. Mooney, Roscoe Pound, Mrs. Ogden Reid, Elihu Root, William Scarlett, Truman G. Schnabel, M.D., Mrs. F. A. Vanderlip, John G. Winant, and Elizabeth F. Read. These persons are of wide experience and recognized as public-spirited citizens.

This movement by the Foundation seems to indicate that the medical profession and coordinate organizations have not found a satisfactory solution of questions of common interest relating to medical service and is a confirmation of the prediction that the public will in time turn its attention to this essential contribution to human welfare.

Although organized medicine has adopted principles designed to govern its application to the ills of mankind and many experiments are underway, there is confusion in the minds of many as to details of procedure, so that a movement of this character warrants endorsement by all parties in interest. The purpose shown by this group is most encouraging. The result of this study is anticipated with the expectation that constructive conclusions will be forthcoming.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

LYON, JAMES A. M.D. Maryland Medical College 1906. F.A.C.P. Cardiologist, Emergency Hospital and Central Dispensary, Columbia Hospital for Women, and The Children's Hospital, Washington, D. C. Professor of Clinical Cardiology, Georgetown University School of Medicine, Washington, D. C. His subject is "Cardiac Pain and Its Significance." Page 953. Address: Washington Medical Building, 1801 Eye Street, Northwest, Washington, D. C.

FLYNN, JOHN M. M.D. Harvard University Medical School 1927. Junior Associate in Medicine, Peter Bent Brigham Hospital. His subject is "A Scheme for the Treatment of Diabetes Mellitus with High Carbohydrate-Low Fat Diets." Page 955. Address: 520 Commonwealth Avenue, Boston, Mass.

LITTLE, RUFUS R. A.B., M.D. University of Pennsylvania School of Medicine 1932. Assistant Physician, North Reading State Sanatorium. His subject is "Artificial Pneumothorax in Adolescents." Page 960. Address: North Reading State Sanatorium, North Wilmington, Mass.

DAMESHEK, WILLIAM. M.D. Harvard University Medical School 1923. Associate Physician, Beth Israel Hospital. Physician, Boston Dispensary. Assistant Professor in Medicine, Tufts College Medical School. Instructor in Medicine, Harvard University Medical School, Courses for Graduates. His subject is "Progress in Hematology. Late 1934 and 1935." Page 962. Address: 371 Commonwealth Avenue, Boston, Mass.

The Massachusetts Medical Society

PROPOSALS FOR LEGISLATION

To the Fellows of the Massachusetts Medical Society:

With the knowledge that the opening of the General Court is but a few weeks away, undoubtedly many individuals have in mind legislation designed to correct injustices or to promote the interests of the medical profession.

Undoubtedly, as in the past, some such legislation will be proposed in good faith and with the best intentions but without thorough study and consideration by the proper committees of the Society.

It is therefore requested that, if the support and backing of the Society are desired by proponents of medical legislation, either individual Fellows, committees or even state departments, that such proposals should be submitted to the Secretary for presentation to the Committee on State and National Legislation for study and report.

CHARLES E. MONGAN, *President*,
Massachusetts Medical Society.

FOURTH ANNUAL POSTGRADUATE MEDICAL EXTENSION COURSE

The following sessions have been arranged by the Committee for the week beginning November 23:

Bristol North

(Course omitted this week on account of Thanksgiving.)

Bristol South (Fall River Section)

Monday, November 23, at 4:00 p. m., at the Stevens Clinic of the Union Hospital, Fall River. Subject: Psychiatry: (a) Psychobiology in General Medicine. (b) The Common Neuroses. Instructor: K. J. Tillotson. Howard P. Sawyer, Co-Chairman.

Bristol South (New Bedford Section)

Friday, November 27, at 4:00 p. m., at St. Luke's Hospital, New Bedford. Subject: Diabetes: General Plan for Treatment in Uncomplicated Cases; Diet; Insulin (Regular and Protamine); Exercise. Instructor: H. F. Root. Robert H. Goodwin, Co-Chairman.

Franklin

Wednesday, November 25, at 8:00 p. m., at the Franklin County Public Hospital, Greenfield. Subject: *Complications* of Diabetes and Their Treatment. Coma; Insulin Reactions; Surgery (Gangrene, Carbuncle, Etc.); Marriage and Pregnancy; Tuberculosis and Heart Disease. Instructor: Priscilla White. Halbert G. Stetson, Chairman.

Middlesex North

Friday, November 27, at 7:00 p. m., at St. Joseph's Hospital, Merrimack Street, Lowell. Subject: Stomach and Duodenal Ulcer: Diagnosis and Treatment. Instructor: E. S. Emery, Jr. Samuel A. Dibbins, Chairman.

Middlesex South

Tuesday, November 24, at 4:00 p. m., at the Cambridge Municipal Hospital, Cambridge. Subject: Anesthesia: (a) Drugs in Anesthesia. (b) General Care of Patient in Anesthesia. Instructor: Joseph Tartakoff. Edmund H. Robbins, Chairman.

Norfolk South

Monday, November 23, at 8:30 p. m., at the Quincy City Hospital, Quincy. Subject: *Complications* of Diabetes and Their Treatment. Coma; Insulin Reactions; Surgery (Gangrene, Carbuncle, Etc.); Marriage and Pregnancy; Tuberculosis and Heart Disease. Instructor: Priscilla White. David L. Belding, Chairman.

Plymouth

Tuesday, November 24, at 4:00 p. m., at the Brockton Hospital, Brockton. Subject: The Physical Examination: Its Scientific, Clinical and Economic Implications. Instructor: L. E. Parkins. W. H. Pulsifer, Chairman.

Worcester North

Friday, November 27, at 4:30 p. m., at the Burbank Hospital, Fitchburg. Subject: Blood Diseases: Diseases Affecting the White Blood Cells. Leukemias; Agranulocytosis; Mononucleosis. Instructor: W. B. Castle. Edward A. Adams, Chairman.

MISCELLANY

DALE AND LOEWI AND THE PREVIOUS NOBEL PRIZE MEN IN PHYSIOLOGY AND MEDICINE

On another page we have commented upon the significance of the Nobel award in Medicine for 1936. It will perhaps interest our readers, however, to have a few further details concerning Professors Dale and Loewi, the latest recipients of the Prize, and a list of the previous awards in the field of physiology and medicine, arranged according to countries.

Henry Hallett Dale, the son of P. J. Dale, was born at London in 1875, and received his primary education at Tollington College, and Leys School (Cambridge); he later attended Trinity College, Cambridge, being as an undergraduate a Coutts-Trotter student, and was later appointed to the George Henry Lewes studentship; at University College, London, he held the Sharpey Scholarship. Dale's clinical training was received at St. Bartholomew's Hospital, but he did not take his degree M.D. till 1909. In 1906 he received the appointment of Director to the Wellcome Physiological Research Laboratories, a post that he continued to hold until 1914. It was during this period that Dale turned his attention to pharmacology and became first interested in the actions of acetyl-choline. He was elected a Fellow of the Royal Society in 1914. During the Great War he was made the head of the department of biochemistry and pharmacology under the Medical Research Council, and he continues to hold this post as Director of the National Institute for Medical Research at Hampstead. Dale was knighted in 1932.

Despite the heavy responsibilities of his secretaryship to the Royal Society, which he has held since 1925, and his membership on the General Medical Council, which he has served since 1927, Professor Dale has continued in active pharmacological investigation and has attracted an increasing body of students. Indeed his laboratory, during the past ten years, has become one of the principal training grounds for European, as well as American, pharmacologists. Dale himself, a Quaker, has an unusual gift of lucid expression, both spoken and verbal. Many in Boston will recall with pleasure his visit at the time of the Physiological Congress in 1929.

Otto Loewi, born June 3, 1873 at Frankfurt-am-Main, received his preliminary education at Strasbourg and Munich, returning in 1896 to Strasbourg to complete his medical studies. He then worked for a year under Carl von Noorden at the Städtisches Krankenhaus at Frankfurt-am-Main. His training as a pharmacologist was received principally from Hans H. Meyer whose Institute in Marburg he entered in 1898 and whom he accompanied to Vienna when Meyer accepted his call in 1905. Loewi was appointed Lecturer at Marburg in 1900 and Professor in 1904. He received a professorship in Vienna in 1906, and in 1909 was called to the Chair of Pharmacology at Graz in southern Austria, which post he has retained until the present time. Loewi, in the course of his active career in experimental pharmacology, has touched nearly all phases in physiology and experimental medicine. In 1908 he published his account of adrenalin mydriasis which is still known as "Loewi's symptom" (*Arch. f. exper. Path., u. Pharmakol.* 150:83, 1908). His other investigations have related to nuclein metabolism, diabetes, renal function, digitalis and the autonomic nervous system. His first paper on humoral transmission, as indicated on another page, was published in 1921. Since that time he has devoted his energies largely to the further analysis of neuro-humoral mechanisms. Many will remember Professor Loewi's Edward K.

Dunham Lectures, given at the Harvard Medical School in May, 1933, in which a full account was given of his investigations in this field.

The Nobel Prize men in Physiology and Medicine are listed below according to countries. It will be seen that Germany still heads the list from the point of view of numbers.

THE NOBEL PRIZE IN PHYSIOLOGY AND MEDICINE

Austria

1914. Robert Barany (Vienna), for his work on the physiology and pathology of the vestibular system. The prize was awarded in 1915.
1927. Professor Julius Wagner-Jauregg (Vienna), for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica.
1936. Professor Otto Loewi (Graz), for studies on neuro-humoral transmission. The prize was shared with Professor H. H. Dale (Great Britain).

Belgium

1919. Professor Jules Bordet (Brussels), for his discoveries in connection with immunity. Awarded in 1920.

Canada

1923. Professor Frederick Grant Banting (Toronto), and Professor John James Richard MacLeod (Toronto), jointly, for the discovery of insulin.

Denmark

1903. Professor Niels Ryberg Finsen (Copenhagen), in recognition of his treatment of disease, especially *lupus vulgaris*, with concentrated light rays.
1920. Professor August Krogh (Copenhagen), for his discovery of the regulation of the motor mechanism of the capillaries.
1926. Professor Johannes Fibiger (Copenhagen), for his discovery of the Spiroptera carcinoma. Awarded in 1927.

France

1907. Charles Louis Alphonse Laveran (Paris), for his work on the part played by protozoa in the generation of disease.
1908. Professor Elie Metchnikoff (Paris), for work (with Professor Ehrlich) on immunity. The prize was divided equally with Professor Paul Ehrlich (Frankfurt-am-Main).

Germany

1901. Professor Emil Adolf von Behring (Marburg), for his work on serum therapy against diphtheria.
1905. Professor Robert Koch (Berlin), for his work on tuberculosis.
1908. Professor Ehrlich (Frankfurt-am-Main), for work (with Professor Metchnikoff) on immunity. The prize was divided equally with Professor Metchnikoff (Paris).
1910. Professor Kossel (Heidelberg), for his achievements in the chemistry of the cell, by his works on proteins, the nucleic substances included.
1922. Professor Otto Meyerhoff (Kiel), for his discovery of the correlation between the consumption of oxygen and the production of lactic acid in the muscles. The prize for the year was divided equally in 1923 with Professor A. V. Hill (Great Britain).
1931. Professor Otto Warburg (Berlin), for his study of the oxidation reduction system of living cells.
1935. Professor Hans Speman, for studies on experimental embryology.

Great Britain

1902. Sir Ronald Ross, for his work on malaria.
1922. Professor Archibald Vivian Hill, for his discovery relating to the heat production of muscles. The prize for the year was divided equally in 1923 with Professor O. Meyerhoff (Kiel).
1929. Sir Frederick Gowland Hopkins, for the discovery of growth-promoting vitamins. The prize was divided equally with Dr. C. Eijkman, Utrecht.
1932. Sir Charles Scott Sherrington and Professor Edgar Douglas Adrian, for elucidation of the functions of the single motor unit in the central nervous system.
1936. Professor Henry Hallett Dale, for studies on neuro-humoral transmission. The prize was divided equally with Dr. Otto Loewi, Graz.

Italy

1906. Professor Camillo Golgi (Pavia), for work (with Professor Ramon y Cajal) on the structure of the nervous system. The prize was divided equally with Professor Ramon y Cajal.

Netherlands

1924. Professor Willem Einthoven (Leyden), for his discovery of the mechanism of the electrocardiogram.
1929. Dr. C. Eijkman (Utrecht), for the discovery of the anti-neuritic vitamin. The prize was divided equally with Sir Frederick Gowland Hopkins (Great Britain).

Russia

1904. Professor Ivan Petrovitch Pavlov (St. Petersburg), in recognition of his work on the physiology of digestion.

Spain

1906. Professor Santiago Ramôn y Cajal (Madrid), for work (with Professor Golgi) on the structure of the nervous system. The prize was divided equally with Professor Camillo Golgi (Pavia).

Sweden

1911. Professor Allvar Gullstrand (Upsala), for his work on the dioptrics of the eye.

Switzerland

1909. Professor Theodor Kocher (Berne), for his work on the physiology, pathology, and surgery of the thyroid gland.

Tunisia

1928. Dr. Charles Nicolle (Tunis), for his work on typhus exanthematicus.

United States

1912. Dr. Alexis Carrel (New York), for his work on vascular ligature and on the grafting of blood vessels and organs.
1930. Dr. Karl Landsteiner (New York), for his work on blood groups.
1933. Dr. Thomas Hunt Morgan (Pasadena), for his investigations concerning the functions of chromosomes.
1934. Professor George Hoyt Whipple (Rochester, N. Y.), Dr. George Richards Minot (Boston), and Dr. William Parry Murphy (Boston), for their discovery of the value of liver in pernicious anemia.

J. F. F.

CONNECTICUT NEWS

Tuberculosis in Hartford

The Hartford Courant of October 24, 1936, in an editorial entitled "Too Much Tuberculosis," advises its readers that seventy-nine persons died of tuberculosis in Hartford during 1935, a figure much too high. The Board of Health has voted to put forth new efforts to reduce this mortality. Dr. Horning, City Health Commissioner, has appointed a committee consisting of Dr. William M. Stockwell, Superintendent of Cedarcrest Sanitarium; Dr. James F. Murphy, president of the Hartford Tuberculosis and Public Health Society, and Dr. Philip F. Parshley, physician in charge of a special tuberculosis project in one of the public schools. The committee has already declared the present program inadequate and believes it necessary to develop a clinic around a hospital where x-ray and fluoroscopic facilities and consultation services are available. A full-time physician will be required to oversee this program but, at present, funds for such a position are available only until July 1, 1937. At present the per capita assessment in Hartford for tuberculosis control is two and one-half cents. In the opinion of Dr. Horning it should be doubled in order to execute an adequate program. Dr. Maxwell O. Phelps will resign the position as part-time director of the tuberculosis bureau of the Board of Health when a full-time director is appointed.

Whooping Cough Outbreak

During October, Hartford and New Britain were the centers of an outbreak of whooping cough, fifty-five new cases being reported in the state in one week, almost two-thirds of which occurred in these two cities.

Lobar Pneumonia Increasing

During the present year, with the season of greatest incidence to come, lobar pneumonia is on the increase in Connecticut. For the three weeks ending October 24, there were sixty-four cases reported as compared with thirty cases for the corresponding three weeks in 1935.

Hartford Retreat to Build Addition

The Neuro-Psychiatric Institute and Hospital of the Hartford Retreat has filed an application for permission to erect a new building at a cost of $16,000. This building will provide for a boiler plant, a barber shop and a print shop.

Newington Home for Crippled Children

A new building housing a department for the care of infants and children under two years of age and an isolation department and adequate facilities for the reception of new children were cited as the outstanding needs at the Newington Home for Crippled Children by its superintendent in her annual report before the board of directors recently.

Dr. Ralph E. Kendall, pathologist, was appointed by the Medical and Surgical Staff to fill the vacancy caused by the resignation of Dr. Wilmar M. Allen. Dr. E. Myles Standish, dermatologist, was appointed to succeed the late Dr. Dwight W. Tracy.

The hospital has increased its service during the past year more than ever before in its history. A total of 74,045 days' care was given to children from 120 communities. Four hundred and fifty patients were cared for free of charge at the triweekly clinics. The physical therapy department gave 18,894 treatments during the year, 1811 of these to outpatients. These free treatments entailed a heavy financial burden because of steadily rising costs in equipment and salaries.

Dr. Wilmar M. Allen, recently appointed Director of the Hartford Hospital, was tendered a dinner on November 5, 1936, by friends on the hospital staff. Dr. Claude W. Munger of Grasslands Hospital, New York, president of the American Hospital Association, was the guest speaker. Colonel Louis R. Cheney, president of the board of directors of the hospital, made some fitting remarks. More than one hundred and thirty physicians attended.

Dr. Valerian S. Michalowski, of New Britain, a captain in the Medical Corps Reserve, has accepted six months' active duty as camp surgeon with the Civilian Conservation Corps and has been detailed to Fort Williams, Maine.

Dr. Thomas G. Sloan, aged 61 years, who had practiced medicine in Manchester for almost thirty-three years, died suddenly of heart disease at his home on October 30, 1936. Dr. Sloan began his practice in Manchester in 1903 when he succeeded to the practice of Dr. Mark S. Bradley. Dr. Sloan was a native of New Haven, studied medicine at Yale and

then at the College of Physicians and Surgeons of Columbia University, New York. He received his medical degree in 1899 and served for one year as intern at the New Haven Hospital. Practicing for a year and a half in New Haven, he then moved to Manchester. Dr. Sloan is survived by his widow and daughter in Manchester, and a sister in New Haven.

Dr. A. Elizabeth Ingraham, Director of the Bureau of Child Hygiene of the State Department of Health since 1923, has resigned, effective January 1, 1937. Dr. Ingraham will retire from active public health work. From a small beginning the well-child conferences, of which Dr. Ingraham has charge, have grown until there are more than eighty now held regularly in various parts of the state. Dr. Ingraham joined the State Department of Health after several years in private practice, two years of which she served the Serbian government in medical work immediately after the World War. She also held the position of resident physician for a short period at the State Farm for Women. In Serbia, Dr. Ingraham founded a hospital for the government and organized a training school.

TUFTS COLLEGE MEDICAL SCHOOL

The following promotions have been made on the Faculty of Tufts College Medical School:

Dr. James J. Hepburn, Professor of Surgery, to succeed Dr. Horace Binney, now Professor-Emeritus of Surgery.

Dr. Benjamin Sachs, Professor of Ophthalmology, to succeed Dr. Edward K. Ellis, now Professor-Emeritus of Ophthalmology.

Dr. James M. Baty, Assistant Professor of Pediatrics.

Dr. Francis C. McDonald, Assistant Professor of Pediatrics.

Dr. Arthur Berk, Assistant Professor of Psychiatry.

Dr. Otto J. Hermann, Clinical Professor of Surgery.

Dr. Harry H. Powers, Assistant Professor of Biochemistry.

Dr. Frederick W. Stetson, Professor-Emeritus of Medicine.

Dr. Louis A. O. Goddu, Clinical Professor of Orthopedics.

Dr. Armin Klein, Clinical Professor of Orthopedics.

Dr. John D. Adams, Assistant Professor of Orthopedics.

New appointments to the Faculty of Tufts College Medical School are as follows:

Dr. John L. Jacobs, Associate Professor of Bacteriology.

Dr. William E. Browne, Clinical Professor of Surgery.

Dr. Archibald McK. Fraser, Clinical Professor of Surgery.

Dr. Andrew R. MacAusland, Clinical Professor of Orthopedics.

Dr. W. Russell MacAusland, Clinical Professor of Orthopedics.

Four Charlton Fund Fellowships have been awarded this year for the second time at the Tufts College Medical School. The stipend of these Fellowships varies from $1200 to $1500 for one year, and the recipients devote their time to teaching and research. It is expected that these Fellowships will be granted every year in the future.

Dr. A. Warren Stearns, Dean of Tufts College Medical School, has been appointed a member of the Staff of *The New England Journal of Medicine*.

The William Harvey Society of Tufts College Medical School again offers a varied program. The lectures are open to all who are interested in the medical profession. Programs of the meetings will appear in this *Journal*.

"Pathfinders in American Medicine," the sixth in a series of annual pageants depicting medical history, was presented by Tufts College Medical School in Jordan Hall, Boston, on November 13, 1936. This year's pageant presented characters from the time of Drs. John Morgan and Benjamin Rush to that of Drs. Reed and Gorgas, and included a portrayal of Marie Zakrzewska, founder of the New England Hospital for Women and Children. The various parts are written and played by students. Past presentations have been published in book form under the title "One Hour of Medical History."

The Tufts College Medical School Journal is opening an exchange system; all medical schools are invited to participate.

Extensive building improvements have been made at Tufts College Medical School; the amphitheater has been converted into additional laboratories for research and demonstration for the Department of Bacteriology.

The number of students in the entering class at Tufts College Medical School has been reduced this year from 125 to approximately 100.

Dr. James Joseph Hepburn has been appointed Professor and head of the Department of Surgery at Tufts College Medical School. He graduated from Harvard College in 1906 and from Harvard Medical School in 1909. He then served a surgical internship at the Boston City Hospital, and began teaching at Tufts College Medical School in the Department of Medicine in 1912. For a number of years he was connected with the Department of Anatomy, and in 1916 he became an instructor in the Department of Surgery. In 1924 he was made an assistant professor, and in 1922 was appointed a clinical professor. Dr. Hepburn has been a Fellow of the American College of Surgeons since 1920.

HONORS CONFERRED ON LORD TWEEDSMUIR AND DR. HENRY A. CHRISTIAN

At the convocation of the Royal College of Physicians and Surgeons of Canada on October 31, 1936, in Ottawa, honorary fellowship was conferred on Lord Tweedsmuir, Governor-General of Canada, and on Dr. Henry A. Christian, Hersey Professor of the Theory and Practice of Physic, Harvard University, and Physician-in-Chief, Peter Bent Brigham Hospital, Boston, Mass.

COMPARISON OF DISEASE INCIDENCE IN CONNECTICUT WITH 1935 AND SEVEN YEAR AVERAGE

MONTH ENDING NOVEMBER 7, 1936

	1936					1935			
Diseases	Week ending Oct. 17	Week ending Oct. 24	Week ending Oct. 31	Week ending Nov. 7	Average cases reported for week corresponding to Nov. 7 for past seven years	Week ending Oct. 19	Week ending Oct. 26	Week ending Nov. 2	Week ending Nov. 9
Actinomycosis	—	—	—	1	—	—	—	—	1
Amebiasis	—	—	1	—	—	1	—	—	—
Chickenpox	23	77	41	101	77	38	83	79	172
Conjunctivitis Infectious	—	—	2	—	—	—	—	2	—
Diphtheria	2	2	2	3	11	5	6	5	2
Dysentery Bacillary	5	1	2	5	1	3	—	—	—
Encephalitis Epidemic	—	—	—	—	—	—	—	1	—
Favus	—	—	—	—	—	1	—	—	—
German Measles	2	5	1	12	1	7	5	—	9
Influenza	3	—	—	3	2	2	—	9	1
Malaria	—	—	1	—	—	—	—	—	—
Measles	8	8	12	36	36	38	58	66	32
Meningococcus Meningitis	1	—	—	—	1	—	—	—	—
Mumps	17	37	40	45	34	20	22	16	70
Paratyphoid Fever	1	3	1	3	—	—	—	—	—
Pneumonia (Broncho)	12	19	21	34	20	12	15	7	16
Pneumonia (Lobar)	18	26	17	35	21	12	18	12	15
Poliomyelitis	1	2	—	—	3	17	9	7	7
Scarlet Fever	15	34	33	50	40	24	44	30	32
Streptococcus Sore Throat	2	2	—	—	1	3	3	1	1
Trachoma	—	1	—	1	—	—	—	—	—
Trichinosis	—	—	—	—	—	1	—	3	—
Tuberculosis (Pul.)	21	29	18	18	24	22	17	28	24
Tuberculosis (O. F.)	1	—	1	1	2	—	—	2	2
Typhoid Fever	1	6	—	—	4	5	1	2	1
Undulant Fever	1	1	1	1	—	2	1	2	4
Whooping Cough	48	74	73	96	46	65	49	71	68
Gonorrhea	41	29	34	50	34	37	43	61	32
Syphilis	63	38	46	45	50	43	62	63	38

Remarks: No cases of Asiatic cholera, glanders, plague or yellow fever during the past seven years.

DR. MAUDE ABBOTT HONORED

On October 23, the doctorate of laws of McGill University was conferred on Dr. Maude Abbott, formerly professor in the faculty of medicine.

THE APPOINTMENT OF MISS MULVILLE

Miss Josephine A. Mulville has been appointed Superintendent of the New England Hospital for Women and Children.

Miss Mulville has been serving as assistant superintendent and principal of the school of nursing at the Beth Israel Hospital. She has had a long experience in administrative positions since her graduation from the Massachusetts General Hospital School of Nursing in 1913, for she was, for two years, the night supervisor of the obstetrical department of the Holyoke City Hospital; for one year assistant superintendent of nurses in the Brooklyn Hospital, New York; four years as superintendent of the Framingham Hospital; three years as superintendent of nurses at the Indianapolis City Hospital, and in the World War twenty-two months in the Base Hospital No. 6.

The New England Hospital for Women and Children is fortunate in securing Miss Mulville.

"CHIROPODY"

Under the Massachusetts statute "Chiropody" means the external treatment of the structures of the human foot by medical, mechanical or surgical means without the use of other than local anes-

thetics. Any person who practices chiropody in this State, with the exception of United States army, navy or marine surgeons and duly registered physicians, must be licensed as a chiropodist. The licensing and regulations of chiropodists is in the jurisdiction of the Board of Registration in Medicine.

Because of this law, care should be taken in the advertising and rendering of services of shoe experts who are not licensed as chiropodists. As the law indicates, shoe fitters have no right to give external treatments of the structures of the human foot by medical, mechanical or surgical means.—*Bulletin, Boston Better Business Bureau*, Vol. IX, No. 17.

THE RIBERI PRIZE AWARDED TO DR. PENTIMALLI

The Riberi Prize founded by an Italian surgeon has been awarded to Dr. Francesco Pentimalli, professor of general pathology at Florence, for his work on experimental tumors and cancer.

RECENT DEATH

PHILLIPS—Frank Elmer Phillips, M.D., of North Chelmsford, Massachusetts, died August 27, 1936.

Dr. Phillips was born in 1871 and graduated from the College of Physicians and Surgeons of Baltimore in 1903. He was a Fellow of the Massachusetts Medical Society and the American Medical Association.

NOTICES

A WARNING TO PHYSICIANS

The Massachusetts Medical Society has been advised by the Boston office of the United States Secret Service, Division of the Treasury Department, to warn all physicians to be on the lookout for a man who has been victimizing the physicians in New York City.

He is described as being short, heavy-set, 5 ft. 8 in. tall, weight about 212 lbs., age about 39 years, black hair and brown eyes. He is said to speak with a pronounced Greek accent and, so far in his dealings, has used the name of George Alexander. His procedure is to consult the physician for a physical examination and upon completion of this give a counterfeit twenty-dollar bill in payment. This bill is said to be a dangerous counterfeit and suspicious physicians should carefully note the serial numbers which may be rather light in color and somewhat irregular both as to impression and alignment.

Physicians are asked to notify the nearest police officer and request him to get in touch with the Secret Service office in Boston.

ANNOUNCEMENT

Miah H. Rovner, M.D., announces the opening of an office at 660 Main Street, Melrose, Massachusetts.

CORRECTION

November 12, 1936.

Editor, *New England Journal of Medicine*,

Dr. Necheles has called my attention to the fact that in the abstract of his article on the "Action of Oil of Peppermint on the Secretion and Motility of Stomach in Man," which was printed on page 718 of the October 15 issue of *The New England Journal of Medicine*, I inadvertently used "healing time" instead of "emptying time."

The statement should have read, "They find that it tends to decrease the secretion of acid and that the emptying time is shortened."

I will appreciate it if you would print this letter in order to correct this unfortunate mistake.

Very truly yours,

Edward S. Emery, Jr., M.D.

319 Longwood Avenue, Boston.

LAWRENCE CANCER CLINIC

Established April 17, 1928

Lawrence, Mass., November 18, 1936.

To the Physicians of the North Half of Essex County:

Dear Doctor:

The regular Lawrence Cancer Clinic, to be held at Lawrence General Hospital, 1 Garden Street, Lawrence, upon Tuesday, December 1, at 10:00 a. m., will be a Demonstration Clinic, for physicians, with Channing C. Simmons, M.D., of Boston, Associate in Surgery in the Graduate Courses in Medicine at Harvard University Medical School, Surgeon-in-Chief to Collis P. Huntington Memorial Hospital, member of the Cancer Commission of Harvard University, Boston, and Visiting Surgeon to the Massachusetts General Hospital, present as consultant. You are invited to accompany any of your patients whom you desire shall have this service, or to send them with a note, and a report will be returned to you. The service is gratis. Your attendance at the Clinic is always welcome.

This clinic is endorsed by the Committee on Postgraduate Instruction of the Massachusetts Medical Society.

Committee

Roy V. Baketel, M.D.
Chas. J. Burgess, M.D.
John J. McArdle, M.D.
Harry H. Nevers, M.D.
Thos. V. Uniac, M.D.
J. Forrest Burnham, M.D., *Chairman*.

WACHUSETT MEDICAL IMPROVEMENT SOCIETY

A course of four lessons in Parliamentary Law for Physicians will be given at Holden District Hospital by Charles W. Proctor, Esq. The first lecture will be Tuesday, November 24, 1936, at 8 p. m., entitled "Parliamentary Conduct of Members at Meetings". Physicians who are not members, and nurses, are invited to attend the course.

REPORTS AND NOTICES OF MEETINGS

THE NEW ENGLAND HEART ASSOCIATION

The first meeting of the New England Heart Association for this season was held at the Massachusetts General Hospital on Monday evening, November 9.

The Speed of Healing of Myocardial Infarction

Drs. Paul White, Jorge Salcedo, and Kenneth Mallory presented a preliminary report on a study of the speed of healing of myocardial infarction. The following criteria were considered essential: (1) a clear history of only one attack of coronary thrombosis in the past with or without a new attack just prior to death, (2) a good description of the macroscopic appearance of the heart, or the availability of the heart itself for study, (3) a good histologic section of the infarct itself for detailed study. Only a small group of cases that fitted these criteria was discovered in their private records and in the clinic at the Massachusetts General Hospital. Hence, further information was sought from some of the other large hospitals in Boston, the Peter Bent Brigham, the Boston City, and the Beth Israel. Altogether some 95 cases were selected; on closer scrutiny some of these will have to be omitted.

All the cases were divided primarily into groups according to the interval of time between coronary thrombosis and death. There were 5 patients who died during the first day, 6 during the second day, 7 during the third day, 5 during the fourth day, 5 during the fifth day, 2 during the sixth day, 4 during the seventh day, 22 during the second week, 7 during the third week, 7 during the fourth week, 7 during the second month, only 1 during the third month, only 3 during the fourth month, only 5 during the next eight months, and 9 after one year.

The great majority of the 86 cases that died within one year were male, 66 in contrast to 20 who were female. The average age of the entire group was in the late 50's, without much difference among the various subgroups designated above. Many of the deaths were sudden; among the 86 who died during the first year 36 died suddenly, 32 died in congestive heart failure, and the other 18 died of other causes. The majority of the infarcts were located in the region of the apex of the left ventricle and were large. The ratio of the acute infarcts at the apex of the left ventricle to those at the base among the patients dying within the first six months was approximately 10 to 1, and it was of interest that, among a considerable number of those dying with acute infarction at the apex of the left ventricle, there was an old healed scar at the base of the left ventricle with or without the clinical history of the past occurrence of such a lesion. Ten of the 86 cases dying within one year showed rupture of the heart wall, 8 had distinct cardiac aneurysms, 47 had intracardiac thrombi overlying the infarcted endocardium (large in 31), and 23 showed acute pericarditis. The heart weights were above normal in nearly all, averaging somewhere about 500 grams in those who died within a year.

Macroscopically the infarct was described as dark red, purplish, brownish red, or dark brown in practically all the cases dying within 2 or 3 months of the onset of illness, and as gray or white in those dying later. The weakest part, however, of the study to date appears right here, for there were only 6 cases in the very important and critical period between 2 months and 6 months after the onset of the acute illness. It was thought that it would be difficult to get many cases at this stage for evidently most patients who recover from the acute and subacute stages of myocardial infarction live out the rest of the year. The myocardial infarct was almost invariably soft in the first 3 months and the consistency was hard after 3 or 4 months.

The microscopic appearance of the infarct was discussed by Dr. Mallory who had made an interesting test in each case by estimating, from the appearance of the section, the length of time from the beginning of the lesion. He had graded them as follows: (1) the reaction and death of the heart muscle cells as the result of the blocking of the blood supply in the first 24 or 48 hours before the appearance of any invading cells, (2) the invasion of multitudes of white cells which come to clear away the débris of the very necrotic myocardium during the first week after the initial 24 to 48 hours, (3) the stage of rapid disappearance of the damaged muscle cells, and replacement of polymorphonuclear cells by mononuclears, and new vascularization of the infarct in the second week, (4) the laying down of the scar with the beginning of the appearance of collagen in the third and fourth weeks, and (5) the complete healing of the scar with much collagen after 2 or 3 months.

Dr. Mallory has been able to estimate the age of the infarct quite accurately in this way provided he is given a section from near the periphery of the fresh infarct. He has found considerably delayed healing in the center of a large infarct.

In conclusion, this preliminary study supports the clinical impression that fairly complete healing of an uncomplicated myocardial infarct of average size takes place in the course of 2 months.

Dr. White next reported a new record in longevity after coronary thrombosis in the case of a clergyman dying at 73 years of age of congestive heart failure, who had his first attack of coronary thrombosis at the age of 48, a second attack at the age of 51, a third attack at the age of 59, and a fourth attack at the age of 63. He died in the twenty-fifth year after the first attack of coronary thrombosis. Postmortem examination showed multiple areas of infarction of the left ventricle.

Dr. White also reported the case of a woman 22 years old with myocardial infarction indicated by clinical and electrocardiographic evidence, in the second month of pregnancy. There has been complete

and satisfactory convalescence without interruption of normal pregnancy. This is apparently the youngest woman ever known to have had coronary thrombosis.

Coronary Disease in Youth

BY R. EARLE GLENDY, M.D., AND PAUL D. WHITE, M.D.

This report deals with a comparative study of serious coronary disease (coronary thrombosis or uncomplicated angina pectoris) in a considerable number of persons under the age of 40 years; first, with those of all age groups who have had serious coronary disease, and secondly, with a group of some 300 very old persons, ranging in age from 80 to 105 years and for the most part in good health. A comprehensive questionnaire has been used to obtain data regarding place of residence, race stock, family history, occupation, nervous strain, diseases, personal hygiene and habits, diet, body build, and economic status. The male sex is overwhelmingly the victim of coronary disease in early life. Residence among the young group was almost wholly urban in contrast to the aged folk who have resided in town or country. Five cases of coronary thrombosis under the age of 30 were of Jewish ancestry. The ancestral longevity in the young group was, as anticipated, less than in the aged group. Occupations were more sedentary, nervous strain and sensitiveness more prevalent, and tobacco and alcohol were used more freely among the young group. The older group claims to have eaten more moderately and exercised with greater regularity. Very few of either group were fat. The two groups, for the most part, claimed to be of moderate means. Infections do not seem to play much of a role in the production of serious coronary disease.

The percentage of survivors is greater and the duration of survival longer, other things being equal, in cases of coronary thrombosis before the age of 40 than in cases of coronary thrombosis of all age groups.

The Effect of Tobacco Smoke on the Electrocardiogram

Dr. Ashton Graybiel discussed electrocardiographic changes following the inhalation of tobacco smoke. He had found that 20 of 45 individuals tested showed some modifications of the QRS and T waves and of the P-R interval. These modifications are usually small but exceptionally there is flattening or inversion of the T waves in Lead 1 or Lead 2 and increase of the P-R interval beyond the normal. These changes he ascribed to the characteristic action of nicotine on the autonomic ganglia.

The Heart Fifteen to Twenty Years After Severe Diphtheria

BY WILLIAM PAUL THOMPSON, M.D.

Ten years ago Jones and White examined 100 people who had had severe diphtheria 5 to 8 years before, and found no evidence of heart disease on examination or of conduction disturbances in the electrocardiograms. Ninety-four of these cases have been followed recently. Two are dead, one of rheumatic heart disease and one of pneumonia. Two are well according to their own statements. Ninety we have now re-examined. An additional group of ten people who had diphtheria of similar severity at the same time has been examined, so that the present total of examined cases is again 100. Two of these have rheumatic heart disease and two have mild hypertension. The others are clinically well. None have A-V block. Four have questionable widening of the QRS complexes with prominent or slurred S-waves in lead II. In two of these cases there has been no change in the electrocardiogram since 10 years ago, while in the other two the width has increased very slightly. These four electrocardiograms are still only suggestively abnormal.

It is very unlikely that diphtheria is responsible for progressive changes in the heart resulting in the delayed appearance of heart block.

The Electrocardiogram in the Newborn Infant With Special Reference to the Technic and to the Chest Lead

BY ROBERT EARLE GLENDY, M.D. AND MARGARET MORIARTY GLENDY, M.D.

The difficulties encountered in taking electrocardiograms on infants and small children can be minimized with the use of special infant electrodes and straps which fit snugly, insuring good electrical contact and causing less restraint and struggling than is encountered when the heavy adult electrodes are used. Infant electrodes of the same material and proportions as those now in common use for adults may be obtained cheaply. Small elastic or rubber straps of suitable size for the extremities and chest may be easily improvised.

In a series (to date) of 69 new-born infants at the Baker Memorial Hospital Nursery, ranging in age from 2 to 17 days, right axis deviation and slight sinus arrhythmia have been invariably present. The average pulse rate has been 150, with extremes of 100 (in one child who was jaundiced) and 187.

The average size and duration of the various complexes in the conventional leads have been much less than the corresponding average figures in adults, due to the smaller heart size and the rapid rate.

The chest lead in the newborn infant differs in no essential way from that of adults except for the T waves, which, in about 60 per cent of the cases, show an upright phase (occasionally diphasic) averaging +2.1 mm. above the isoelectric level. About 25 per cent are downwardly directed (averaging —1.5 mm. below the isoelectric level) and the remainder are either flat or very poorly marked.

The Growing Importance of Cardiac Neurosis

Dr. White concluded the meeting with a statement concerning the growing importance of cardiac neurosis. The more heart disease there is, and especially the more widespread the publicity about it, the more important is the problem of cardiac neurosis or

cardiac psychoneurosis which is not to be confounded with neurocirculatory asthenia.

Cardiac neurosis is always based on some very definite exciting factor such as the occurrence of heart disease, especially heart deaths among family and friends, or simply reported in the newspapers under dramatic headlines, the finding by a physician of a heart murmur, trivial or not, of some disturbance of rhythm which may be insignificant, of hypertension great or small, or of actual heart disease. The findings on x-ray examination or in the electrocardiogram have in some cases initiated a cardiac neurosis. Subjective sensations may be the starting point, a disagreeable extrasystole, a paroxysm of tachycardia, the manifold symptoms of neurocirculatory asthenia, sighing respiration, true dyspnea, angina pectoris, the prolonged pain of coronary thrombosis, and various pains in the center or left side of the chest of noncardiac origin, due to cardiospasm, bursitis, muscle strain, and pleurisy among others.

The most difficult cases are those with serious heart disease complicated by cardiac neurosis. Dr. White stated that it was a common experience in his practice that nervous prostration or a severe cardiac psychoneurosis following coronary thrombosis, especially in physicians, was often more difficult to treat than the myocardial infarction itself.

FAULKNER HOSPITAL CLINICAL MEETING

The regular monthly clinical meeting was held at the Faulkner Hospital on Thursday afternoon, November 5, at 5:00 p. m.

The first case which had come to autopsy that was brought up for discussion was that of an eighty-three year old woman who had given a history of indigestion for some years for which she had taken an appreciable amount of patent medicine and consulted many doctors, frequently more than one at a time but had rarely followed their advice and had specifically refused to follow the recommendations of her last physician which were to have her come into the hospital for study.

Six days before entrance she began to vomit and had epigastric pain and diarrhea. The epigastric pain and diarrhea soon subsided but the vomiting persisted.

The physical examination showed a small, emaciated, old woman with a dry tongue and an abdomen which was not distended although some high-pitched peristaltic sounds were heard on auscultation. Her blood pressure which formerly had been elevated was 112 systolic over 68 diastolic. The urine showed a large amount of albumin and casts with a trace of acetone. There was a mild leukocytosis and no appreciable anemia. The vomitus was brownish in color and had a fecal odor. The stools showed some occult blood. Her blood sugar was just above the normal limits but the nonprotein nitrogen showed 200 mgm. per 100 cc.

An attempt to study the gastrointestinal tract with barium enema was unsuccessful because the barium could not be retained and it was impossible to insert it beyond the sigmoid flexure. A picture of the abdomen showed distended loops of small intestine. The extreme right side of the patient's abdomen was not seen on the film.

The diagnosis rested between an intestinal obstruction, presumably fairly high because of the increased nonprotein nitrogen in the blood, or a terminal uremia. It was difficult to understand why the abdomen was not more distended if it was an intestinal obstruction. The patient quickly succumbed after her entrance to the hospital and at autopsy there was an obstruction in the small intestine near the ileocecal valve caused by a large gallstone which had entered the intestine through a fistula between the gallbladder and the duodenum. The kidneys were found in fairly satisfactory condition for a person of her age. Although the gallstone obstructed the bowel, it at times permitted gas to pass by which accounted for the lack of distention.

The second case was that of a man forty-seven years of age who had been running a fever for a year and gradually losing flesh and strength. In the past he had had dysentery and malaria, and there was a question of tuberculosis as a cause for his father's death.

His illness started with pain in the right shoulder which did not cause limitation of motion, nor was it aggravated by motion. At this time he found that he tired more easily and that he was running a fever which ranged from 99° to 103°.

Finally an x-ray picture of the chest was taken which showed a shadow at the right apex. It was thought that the patient probably had tuberculosis and for two months he stayed in bed without improvement, during which time he gradually lost thirty pounds in weight. There was no cough or expectoration. There were night-sweats which might have been due to medication. After 3 months on this program he came to the hospital for more elaborate studies. The only positive findings on physical examination in addition to the loss of weight were slight clubbing of the fingers and the fact that the right chest at the apex region did not move so much as the left on deep inspiration.

The routine clinical pathology, except for a mild secondary anemia and a mild leukocytosis, was entirely negative. Blood cultures were negative. The Hinton test was negative. The agglutination tests for tularemia and undulant fever were negative. An unsatisfactory sputum specimen showed no tubercle bacilli. The skin tuberculin test was negative.

A great number of x-ray pictures were taken, all of which were negative except for a shadow of consolidation at the right apex which did not involve any of the bony structures, an enlarged liver according to a flat film of the abdomen and a gallbladder which did not fill after taking the dye by mouth. At this time tuberculosis was considered the correct diagnosis by some, and some type of neoplasm, possibly Hodgkin's disease by others. On the faint chance that there might be a liver abscess associated with the old dysentery or more involvement of the gallbladder than was apparent clinically, it

was decided to explore the abdomen, although it was generally felt that the lesion at the right apex was too extensive to be just a healed process. At the exploration the liver was found to be essentially normal and the gallbladder only very slightly thickened and obviously not the cause of his illness.

A month after admission to the hospital the shadow at the right apex was possibly slightly larger than on admission. It was decided to look upon this as a growth and presumably not of the Hodgkin's variety, because at the exploration careful search for lymphoid overgrowths was made and none found. Accordingly x-ray therapy was tried without immediate results and an x-ray of the chest 2 months later showed the shadow certainly no smaller and possibly larger, so further x-ray therapy was given up.

The patient continued to go downhill and died 4 months later with marked emaciation, pronounced secondary anemia, ascites and hydropericardium and edema of the hands and feet, all of which were presumed to be terminal conditions associated with the chemical changes in the body fluids associated with his illness.

At autopsy there was found a carcinoma at the right apex which was markedly necrotic but contained no cavities. This carcinoma originated either from the epithelium of the smaller bronchi or was alveolar in origin. There is still some dispute on this point. It had extended through the pleura and invaded the bones in that vicinity but the invasion of the bones was apparently a development in later months because there was no evidence of bony destruction in the x-ray pictures taken 4 months before his death. There was no evidence of metastasis. There was a small amount of microscopic tuberculosis in one of the lymph glands at the hilus of the lungs but it was felt that this was of no practical importance. No cause for the ascites or hydropericardium was found at autopsy.

At the last examination by x-ray there was a suggestion of cavitation in the dense shadow caused by the tumor. At autopsy there were many emphysematous blebs in the lung tissue surrounding the tumor which may have caused this appearance by x-ray. The striking feature of tumors of this type is the fever and destructive effect upon nutrition caused apparently by the absorption from the necrotic material in the tumor. As pain had developed in the shoulder suggesting invasion of nerves before the fever was discovered, it seems that this case was hopeless from the start so far as surgical intervention is concerned.

Following the discussion of these two unusual and interesting cases, Dr. Harlan F. Newton talked about the practical application in thoracic surgery of the recent advances in diagnosis and treatment. Before doing so, however, he showed x-ray pictures from two cases of neoplasm of the lung which started in the alveoli and emphasized the long-continued fever which had existed in these cases. The clinical picture was very similar to that in the case just presented, although the tumor was in a slightly different part of the lung.

Dr. Newton divided the problems of thoracic surgery into cases with inflammation and tumor and emphasized the fact that improvement in making an early diagnosis and in localizing the lesions and mechanical aids in treatment were tremendous factors in the advances made in this type of surgery.

He called attention to the importance of paying attention to a persistent cough, especially one with a wheeze associated with it. Coughs should also be studied from the point of view of whether they are dry or productive. An unproductive cough which lasts any appreciable time calls for intensive study. Bleeding is a very important symptom in tumor of the lung and occurs in a much higher percentage of tumor cases than in cases of tuberculosis.

In studying diagnostic problems in the lung one should not rely only upon the routine x-ray examination, but must have pictures taken from a variety of angles and must depend in addition upon the fluoroscope.

Dr. Newton was especially enthusiastic about the value of lipiodol injections for localizing the lesion and showed a very striking x-ray photograph after lipiodol injection of a bronchiectasis localized in one lobe of the lung behind the heart, so that it did not appear in the usual x-ray photograph. This patient was relieved by removal of the lobe.

He mentioned the importance of bronchoscopic study not only for diagnosis but also for treatment and called attention to the value of thoracoscopy for diagnosis and also for aid in cutting adhesions to make collapse of the lung more complete in certain cases.

The progress of anesthesia has aided appreciably in the operative procedures upon the lungs.

He likes to think of tuberculosis as a disease that is somewhat destructive but also in its reaction proliferative, and therefore has a chance to heal itself without removing the destroyed products.

The pyogenic infections are usually destructive and the products of these organisms must be removed.

In abscess of the lungs he believes in conservative treatment during the acute stage and considers that the acute stage should be considered to last from 6 to 9 weeks.

Collapse therapy is of value not only in tuberculosis but also in pyogenic infections.

He mentioned figures to show that tuberculosis in young people in their 'teens usually resulted fatally in about 85 per cent within 10 years, showing that immunity is poor at that age. If the outlook is so poor for these patients, he feels that it is well worth while to try some form of collapse therapy either pneumothorax or removal of the ribs to give these young patients a better chance.

While the tuberculosis is acute, major surgery should be avoided.

In chronic tuberculosis with cavitation some type of collapse is of distinct value and Dr. Newton mentioned a case of a fifty-nine year old patient who

had had a cavity with tubercle bacilli in the sputum for years without being able to heal the cavity, and after collapse therapy by removal of some ribs over the apex area the cavity had very promptly and entirely disappeared. The type of operation which is going to be used depends definitely upon the extent of the process and its location in the lungs in chronic tuberculosis. If the process is extensive there must be one lobe of the lung which is definitely shown to be free from activity by x-ray before surgery is undertaken, otherwise a tubercular bronchopneumonia will probably develop in the part of the lung which is least involved.

He called attention to the fact that lobectomy in properly selected cases does not show any higher mortality than that seen in operations upon acute appendicitis, and therefore, the early diagnosis of neoplasms is essential. It is also important in bronchiectatic conditions confined to one lobe to consider the removal of the lobe before the process becomes more diffuse in the lungs.

BOSTON PATHOLOGICAL SOCIETY

The Boston Pathological Society met at the Harvard Medical School Wednesday evening, October 28, 1936, Dr. J. B. Hazard presiding. Dr. E. A. Codman spoke on the subject: "A Study of the Cases in the Registry of Bone Sarcoma of Giant Cell Tumor about the Knee." He spoke of several untreated cases of such tumors that were alive and well twelve and twenty-six years after the diagnosis was made, apparently with little deformity, and with good function of the leg.

A study of the growth characteristics of these tumors has shown that only rarely do they spread upwards into the tubular portion of the bone, and that they are usually limited to the cancellous portion near the old epiphyseal line. Two important characteristics of giant cell tumors were cited: They almost always stop abruptly with a convex border at the margin of the cancellous portion of the bone (or at the metaphyseal line). They expand the wall of the bone and are easily shelled out with the finger at the time of operation. The cartilage of the joint is not destroyed. These facts have led Dr. Codman to believe that giant cell tumors are a form of compound arteriovenous aneurysm. He considers the giant cells to be in reality connected together, while red blood cells circulate freely between their anastomosing processes. This belief is strengthened by the observation that pulsations of the tumor mass occur coincident with the heart beat, and that injection of the arterial system of the leg causes the tumor to be diffusely filled with the injection mass. He does not consider the giant cells to be malignant, and stated that all the cells observed in these tumors are found in normal granulation tissue.

In discussing the treatment of these tumors, Dr. Codman pointed out the futility of implanting bone chips in the cavity after curetting out the tumor, since they are completely resorbed. This resorption occurs because the chips do not lie in any line of stress, and the normal body processes are called into action to remove them in the same way that any foreign body is removed. He advised a new operation in which a flap of the periosteum is placed in the cavity after thorough curetting and establishment of absolute hemostasis. He does not fear leaving some of the giant cells behind, since he does not regard them as malignant. X-rays of a case treated in this manner were projected, showing marked filling in of the defect with solid bone, a condition that never would occur spontaneously because of the destruction of the endosteum by the expanding tumor.

Fractures through these tumors should not be considered as an indication for amputation. In some cases fractures have been known to initiate a healing process, perhaps because of shutting off the blood supply to the aneurysm. X-ray treatment in some cases may produce a similar result.

Giant cell tumors never metastasize. Some 10 per cent undergo malignant change, however, and may cause death because of metastases as sarcoma. Such malignant degeneration is probably brought on by operative interference with the tumor, especially if it be repeated.

Following Dr. Codman's address the meeting was adjourned to an inspection of the histories, x-rays, and specimens of the cases from the Registry of Bone Sarcoma, and to informal discussion.

THE NORFOLK DISTRICT MEDICAL SOCIETY

A stated meeting of the Society will be held in the Beth Israel Hospital, Tuesday, November 24, 1936, at 8 p. m. Telephone Beacon 4400.

Business meeting 8:00 p. m.

Communications: 8:15 p. m.

Clinical Significance of Coronary Artery Anastomoses—Dr. Monroe J. Schlesinger.

Clinical Significance of Insufficient Coronary Blood Flow—Dr. Herrman L. Blumgart.

Medicinal Treatment of Angina Pectoris—Dr. J. E. F. Riseman.

Tobacco and Alcohol in Angina Pectoris—Dr. Louis Wolff.

Effect of Intravenous Fluid on the Cardiovascular System—Dr. Mark H. Altschule.

Pulmonary Complications in Raynaud's Disease—Dr. Harry Linenthal.

Each speaker will occupy twelve minutes.

Collation.

FRANK S. CRUICKSHANK, M.D., *Secretary.*
1247 Beacon Street, Brookline.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The next meeting of this Society will take place on Wednesday, November 25, at the Middlesex County Sanatorium, Trapelo Road, Waltham.

The speaker is Dr. Cole B. Gibson, Superintendent and Medical Director of the Meriden State Tuberculosis Sanatorium.

Dr. Gibson is an outstanding worker in the field

of Tuberculosis. He comes from Connecticut and will deliver a talk that will be most instructive. It is the hope of the officers that a large audience will be present.

Luncheon will be served at 12:15 p. m.

Those attending may be reached by telephone; the number is Waltham 4600.

SUMNER H. REMICK, M.D., *President.*
ALEXANDER A. LEVI, M.D., *Secretary.*

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

The next meeting of the Essex South District Medical Society will be held Wednesday, December 2, 1936, at the Salem Hospital.

Clinic at 5 p. m.

Dinner at 7 p. m.

Speaker: Dr. John W. Strieder, Associate Professor of Chest Surgery, at Boston University School of Medicine.

Subject: "Pulmonary Suppuration."

R. E. STONE, M.D., *Secretary.*

AMERICAN COLLEGE OF SURGEONS

The annual Clinical Congress of the American College of Surgeons will be held in Chicago, October 25-29, 1937.

THE NEW ENGLAND HOSPITAL ASSOCIATION

The New England Hospital Association is having its Fifteenth Annual Meeting at the Hotel Statler, Boston, Massachusetts, on February 25, 26, and 27, 1937.

A. G. ENGELBACH, M.D., *Secretary.*

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held in the Peter Bent Brigham Hospital Amphitheater (Shattuck Street Entrance), Tuesday evening, November 24, at 8:15 p. m.

PROGRAM

Presentation of Cases.

Studies of Renal Physiology. By D. D. Van Slyke, The Hospital of the Rockefeller Institute for Medical Research.

Professor A. Baird Hastings will preside.

Medical students and physicians are cordially invited to attend.

MARSHALL N. FULTON, M.D., *Secretary.*

PHARMACOPOEIAL HEARING IN WASHINGTON

A meeting of those interested in the revision of U. S. P. XI monographs will be held at the Hotel Washington, Washington, D. C. on Monday, November 30, 1936. The sessions will be called at 10 a. m., and 2 p. m.

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, NOVEMBER 23, 1936

Tuesday, November 24—

11:30 a. m. Massachusetts General Hospital. Eye Nerve Conference.

1 p. m. Massachusetts Society for Mental Hygiene. Twentieth Century Club, 3 Joy Street, Boston.

8 p. m. Norfolk District Medical Society. Beth Israel Hospital, Boston.

*8:15 p. m. Harvard Medical Society. Peter Bent Brigham Hospital Amphitheater (Shattuck Street entrance).

Wednesday, November 25—

8 a. m. Massachusetts General Hospital. Grand Rounds, Orthopedic Department.

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Hospital Case Presentation. Dr. S. J. Thannhauser.

†12 m. Clinico-Pathological Conference. Children's Hospital Amphitheater.

4 p. m. - 5 p. m. Surgical Pathological Conference, Dr. Cutler and Dr. Wolbach, Peter Bent Brigham Hospital.

Friday, November 27—

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Practical Considerations of the Cancer Problem. Dr. Robert B. Greenough.

10 a. m. Massachusetts General Hospital. Fracture Rounds.

12 m. Massachusetts General Hospital. Clinical Meeting of the Staff of the Children's Medical Service. Ether Dome.

Saturday, November 28—

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Hospital Case Presentation. Dr. S. J. Thannhauser.

*10 a. m. - 12 m. Staff Rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.

†Open to Fellows of the Massachusetts Medical Society.

November 19—Medical Clinic, Peter Bent Brigham Hospital, 3:30 p. m.

November 20—New England Roentgen Ray Society, 8:15 p. m. Boston Medical Library, 8 Fenway.

November 24—Harvard Medical Society. See notice elsewhere on this page.

November 24—Wachusett Medical Improvement Society. See page 997.

November 24—Massachusetts Society for Mental Hygiene, 1 p. m. Twentieth Century Club, 3 Joy Street, Boston.

November 30—Pharmacopoeial Hearing in Washington. See notice elsewhere on this page.

December 1—Lawrence Cancer Clinic. See page 997.

December 2—New England Obstetrical and Gynecological Society, University Club, Boston.

December 3-5—Annual Conference of the National Society for the Prevention of Blindness, Columbus, Ohio.

December 10—Pentucket Association of Physicians, Hotel Bartlett, 95 Main Street, Haverhill, at 8:30 p. m.

December 11—William Harvey Society. Auditorium, Beth Israel Hospital, Boston, 8 p. m.

December 15—Massachusetts Eye and Ear Infirmary, Monthly Clinico-Pathological Conference. See page 949, issue of November 12.

February 25, 26, 27, 1937—The New England Hospital Association. See notice elsewhere on this page.

March 30 - April 2, 1937—First International Conference on Fever Therapy. Postponement notice. See page 52, issue of July 2.

April 21-24, 1937—American Society for Experimental Pathology. See page 1075, issue of May 21.

October 25-29, 1937—American College of Surgeons. See notice elsewhere on this page.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

December 2—See notice elsewhere on this page.

FRANKLIN DISTRICT MEDICAL SOCIETY

Will meet at the Weldon in Greenfield at 11 a. m. the second Tuesdays of January, March and May.

CHARLES MOLINE, M.D., Secretary.

Sunderland.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

January 13, 1937—Bear Hill Golf Club, Stoneham.
March 16, 1937—Danvers State Hospital, Danvers.
May 11, 1937—Bear Hill Golf Club, Stoneham.

KENNETH L. MACLACHLAN, M.D., Secretary.
1 Bellevue Avenue, Melrose.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

November 25—See page 1002.

NORFOLK DISTRICT MEDICAL SOCIETY

November 24—See page 1002.

January 19, 1937—8:15 p. m. The Peter Bent Brigham Hospital. Communications and Case Presentations by the Staff. Suggested title—"Abdominal Pain from the Medical and Surgical Standpoint." Details of program to be announced.

February 23, 1937—Time, place and details of program to be announced.

March 30, 1937—8:15 p. m. New England Deaconess Hospital. A Symposium on Diabetes entitled "A Survey of the Diabetic Work of the George F. Baker Clinic in the New England Deaconess Hospital." Communications and Case Presentations by the Staff. Drs. Elliott P. Joslin, Howard F. Root, Priscilla White, Alexander Marble and Allen P. Joslin.

May, 1937—Annual Meeting. Details to be announced.

Note: The Censors will meet for the examination of candidates on the first Thursday of May, 1937. Fee of $10.00 is payable at the time of examination. Application blanks may be obtained by writing the Secretary, furnishing name, address and name of school of graduation in medicine. Application must be made at least three weeks prior to date of examination. Candidates whose applications are on file will receive proper notices.

FRANK S. CRUICKSHANK, M.D., Secretary.
1247 Beacon Street, Brookline.

PLYMOUTH DISTRICT MEDICAL SOCIETY

November 19—6 p. m. Goddard Hospital.

January 21, 1937—11 a. m. Bridgewater State Farm.

March 18, 1937—11 a. m. Brockton Hospital.

April 15, 1937—Annual Meeting. 11 a. m. Ducy Hospital.

May 20, 1937—11 a. m. Lakeville State Sanatorium.

FRED F. WEINER, M.D., Secretary.
231 Main Street, Brockton.

SUFFOLK DISTRICT MEDICAL SOCIETY

January 27, 1937—Boston Medical Library. 8:15 p. m. Joint Meeting with the Boston Medical Library. "Anthropology." Dr. Carleton S. Coon.

March 31, 1937—Boston Medical Library. 8:15 p. m. "Social Insurance—It Affects the Medical Profession." Dr. Charles E. Mongan. Discussion: Dr. Channing Frothingham.

April 28, 1937—Annual Meeting. Boston Medical Library. 8:15 p. m. "Problems in Surgical Diagnosis." Dr. Howard M. Clute.

CONRAD WESSELHOEFT, M.D., President,
CHARLES C. LUND, M.D., Secretary.

WORCESTER DISTRICT MEDICAL SOCIETY

December 9—St. Vincent Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

January 13, 1937—Worcester City Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

February 10, 1937—Worcester State Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

March 10, 1937—The Memorial Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

April 14, 1937—Worcester Hahnemann Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

May 6, 1937—At 4:30 in the rooms of the Worcester Medical Library, Inc., at 34 Elm Street, Worcester, will be held the spring meeting of the Board of Censors.

Wednesday Afternoon and Evening, May 12, 1937—Annual Meeting. Time and place for this meeting will be announced in an early spring issue of the Journal.

ERWIN C. MILLER, M.D., Secretary.
27 Elm Street, Worcester.

BOOKS RECEIVED FOR REVIEW

Eugenical Sterilization. A Reorientation of the Problem. By the Committee of the American Neurological Association for the Investigation of Eugenical Sterilization. 211 pp. New York: The Macmillan Company. $3.00.

The Intellectual Functions of the Frontal Lobes. A Study Based Upon Observation of a Man After Partial Bilateral Frontal Lobectomy. Richard M. Brickner. 354 pp. New York: The Macmillan Company. $3.50.

Modern Urology. In original contributions by American authors. Volume I. General Considerations—Diseases of Penis and Urethra—Diseases of Scrotum and Testicle — Diseases of Prostate and Seminal Vesicles. Edited by Hugh Cabot. Third Edition, Thoroughly Revised. 951 pp. Philadelphia: Lea & Febiger.

Modern Urology. In original contributions by American authors. Volume II. Diseases of the Bladder—Diseases of the Ureter—Diseases of the Kidney—Radiation Therapy of Tumors of the Genito-Urinary Tract. Edited by Hugh Cabot. Third Edition, Thoroughly Revised. 862 pp. Philadelphia: Lea & Febiger.

Textbook of General Surgery. Warren H. Cole and Robert Elman. 1031 pp. New York and London: D. Appleton-Century Company. $10.00.

Text-Book of Pathology. Sir Robert Muir. Fourth Edition. 994 pp. Baltimore: William Wood & Company. $10.00.

A Practical Medical Dictionary. Thomas Lathrop Stedman. 1291 pp. Thirteenth, Revised, Edition. Baltimore: William Wood & Company. $7.50.

British Masters of Medicine. Edited by Sir D'Arcy Power. 242 pp. Baltimore: William Wood & Company. $3.00.

Bailey's Text-Book of Histology (Elwyn and Strong). Revised and Rewritten by Philip E. Smith. 773 pp. Ninth Edition. Baltimore: William Wood & Company. $6.00.

Urological Roentgenology. A Manual for Students and Practitioners. Miley B. Wesson and Howard E. Ruggles. 269 pp. Philadelphia: Lea & Febiger. $5.00.

BOOK REVIEW

An Introduction to Materia Medica and Pharmacology. Hugh A. McGuigan and Edith P. Brodie. 580 pp. St. Louis: The C. V. Mosby Company. $2.75.

This book might be entitled "A Pharmacologist Revises a Nurses' Textbook of Pharmacology." The revision is apparently a very extensive one, and the book is now really McGuigan's and not Miss Brodie's. McGuigan, in his preface, emphasizes the fact that pharmacologic teaching even to nurses should depend to great extent upon animal experimentation. A plea is also made for the use of standard preparations and for the diminution of obsolete and proprietary medications. The book in its present form is intensely practical, very readable, and might even be of value to medical students and physicians as well as to nurses—for whom it was primarily written. In some respects, particularly in readability, practicality, and excellence of illustrations, it surpasses standard texts of pharmacology. One has no hesitancy in recommending this book highly to the nurses' teaching profession.